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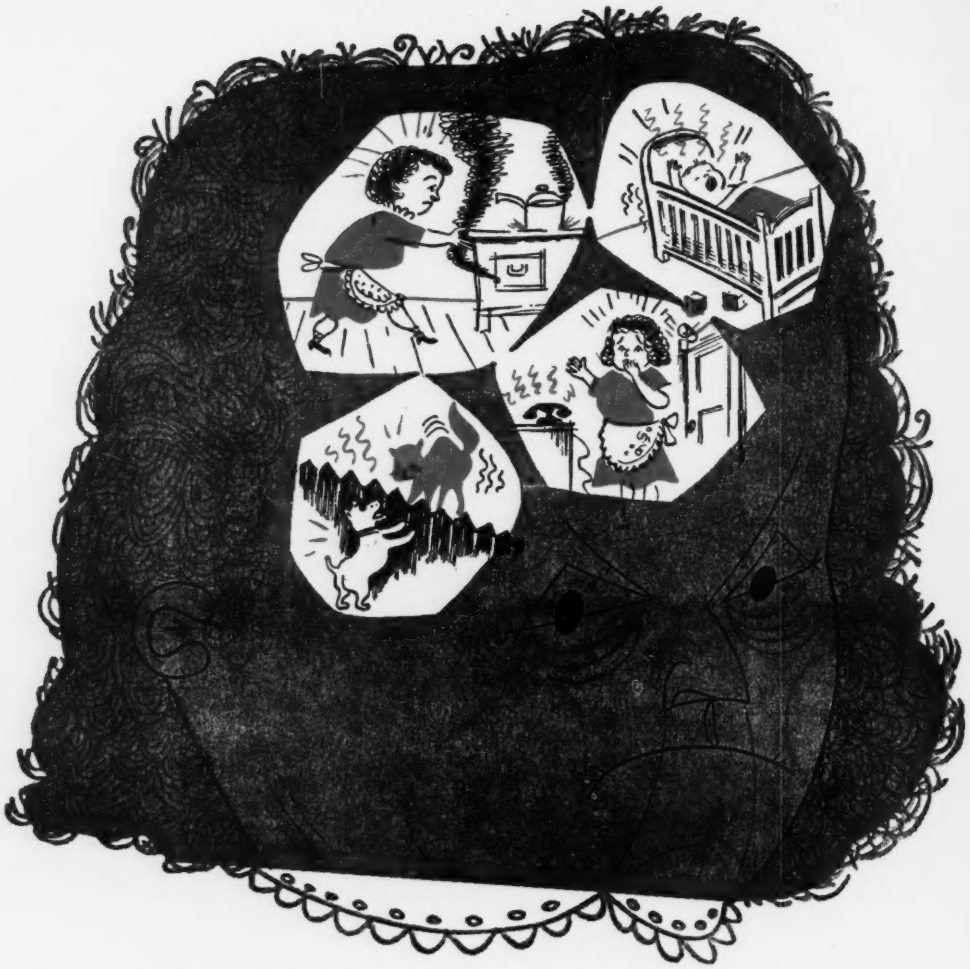

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Circulation

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VOL. XIV NO. 2

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

"Serotonin" or "Tenure for the Pharmacologist"

IN RETROSPECT, serotonin made its debut to science in 1868, when it was noted that defibrinated blood caused vasoconstriction. Not until 1948 was it isolated as a substance released with clotting of blood. Then, in 1951, serotonin was synthesized as 5-hydroxytryptamine. The 5 succeeding years have seen development of the greatest interest in the drug by both basic and clinical scientists. And rightly so, when it is recalled that another vasoconstrictor substance, norepinephrine, has only recently been firmly established as an important humoral mediator. Recent studies indicate that serotonin may have several highly important roles in physiology and pathology. Here is a sampling of these studies, first as regards possible roles of serotonin in cardiovascular physiology and pathology and then as regards central nervous system function. (Detailed reviews and bibliography appear in articles by Page[1] and Erspamer.[2])

The vasoconstrictor action of serotonin was the first one described and is the best known. While little serotonin is found in normal circulating blood, it may occur in special sites in amounts sufficient to cause vasoconstriction. The most common such event is in association with clotting of blood. Local high concentrations may occur otherwise, however, and be of both physiologic and pathologic significance. It has been suggested, for instance, that the severe widespread, and sometimes fatal, pulmonary vasoconstriction following pulmonary embolus may be due to release and spread of serotonin. To support this hypothesis is the observation that infarction of pulmonary tissue with starch is a more benign procedure than infarction of an equal area of pulmonary tissue with clotted blood. Since serotonin also has a coronary vasoconstrictor action, a similar deleterious effect may follow myocardial infarction, as well as embolus and infarction in other parts of the body.

The usual effect of very small doses of serotonin injected intravenously is vasodilatation and fall in arterial pressure, as long as there is pre-existing significant neurogenic vasoconstriction; in the absence of the latter, serotonin is vasoconstrictor and pressor. The important problem of whether serotonin may participate in regulation of blood flow by influencing neurogenic vasoconstriction awaits solution. The vasodilatation that follows intravenous injection of serotonin is antagonized by vasoconstriction and cardiac acceleration from stimulation of carotid and aortic chemoceptors. That serotonin is an even more powerful chemoceptor stimulant than lobeline in dogs is an unexpected and intriguing finding.

Serotonin has also captured the attention of renal physiologists. Whether, as postulated, it is an important hormone regulating renal blood flow is uncertain; but it is certain that when serotonin is infused intravenously in rather large doses, it has a dramatic vasoconstrictor action, sufficient even to cause cortical necrosis. In this way it might contribute to the renal damage associated with eclampsia. Present in any significant quantities in circulating blood, serotonin may well have powerful effects on renal hemodynamics.

An odd syndrome attributable to serotonin occurs in some patients with malignant carcinoid tumors. The usual, but not invariable, features are a cyanotic type of flushing, diar-

rhea, and tricuspid stenosis. A number of these patients have now been described. They secrete large amounts of 5-hydroxyindole acetic acid in the urine and this provides a convenient and reliable method for antemortem diagnosis of metastatic carcinoid. Serotonin has been found in large quantities in the blood of these patients, and there can be little doubt that it plays an important part in the mechanism of the syndrome. Since serotonin has some chemical resemblance to the plant growth hormones, the proliferative response of the endocardium in the right side of the heart suggests an even broader spectrum of effects.

The possible role serotonin might play in the function of the nervous system stems mainly from 3 observations: (1) serotonin is present in the mammalian central nervous system in relatively large amounts; (2) the dimethyl derivative of serotonin, called bufotenine, produces hallucinations and is used in Haiti for that purpose; (3) both the central and peripheral actions of serotonin may be blocked by lysergic acid diethylamide (L.S.D.), which produces severe, schizophrenic-like mental disturbances. We are as yet far from knowing the precise role played by serotonin or other indole derivatives in cerebral function, but current evidence suggests its great importance.

Serotonin is also present in the ganglia of many invertebrates in relatively much greater quantities than acetylcholine. This finding, plus other testimony, has led to the belief that serotonin may be an important transmitter of nerve impulses in autonomic ganglia.

The action of reserpine has been suggested to be due to intermediation of serotonin. After reserpine administration, brain cells seem to lose their power to retain serotonin, with the result that it is liberated from cells and destroyed by monoamineoxidase. Bound serotonin does not seem susceptible to destruction by this enzyme. Another "tranquilizing" agent, chlorpromazine, antagonizes the cardiovascular actions of serotonin.

Serotonin and related indole derivatives have rather suddenly assumed a new importance with discoveries linking them to various bodily functions and dysfunctions. During the next few years, which are assured of being busy ones for both clinical and basic scientists, it will undoubtedly be necessary for all of us to become better acquainted with the multiple facets of their actions. The story of serotonin exemplifies the great importance of isolation, structural identification, synthesis, and, finally, making available to a large variety of investigators substances found in the animal body.

IRVINE H. PAGE
J. W. MCCUBBIN

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[2] ERSPAMER, V.: Pharmacology of indolealchylamines. Pharmacol. Rev. **6:** 425, 1954.

I wish the reader to keep in view, that it is not my intention merely to introduce a new diuretic to his acquaintance, but one which, though not infallible, I believe to be much more certain than any other in present use.

After all, in spite of opinion, prejudice, or error, Time will fix the real value upon this discovery, and determine whether I have imposed upon myself and others, or contributed to the benefit of science and mankind.—WILLIAM WITHERING. *An Account of the Foxglove, and Some of Its Medical Uses.* Birmingham, 1785.

Cardiocirculatory Studies in Pulsus Alternans of the Systemic and Pulmonary Circulations

By M. Irené Ferrer, M.D., Réjane M. Harvey, M.D., André Cournand, M.D., and Dickinson W. Richards, M.D.

Studies carried out in 21 patients have shown for the first time that alternation of the pulse pressure in man can occur independently in either the greater or the lesser circulation without appearing in the other. Even when bilateral alternation exists, this cyclic variation may disappear in one circulation while persisting in the other. Mechanisms responsible for pulsus alternans, in particular variations in stroke volume and vascular pressures, are considered, and no single explanation satisfies the facts revealed in this study.

SINCE Traube's original description in 1872, the term pulsus alternans has been used to describe a special type of cyclic variation in systemic pulse pressure. Considerable clinical importance has since been attached to this circulatory sign, particularly since it is readily elicited with a simple sphygmomanometer. Although much laboratory investigation has been devoted to this subject,[1-5] clinical exploration has been limited to studies of the systemic arteries in man until the advent of cardiac catheterization, when the exploration of both greater and lesser circulations could be made.[6-8]

Prior to the present study, it had been more or less assumed that alternation in arterial pulse pressure was accompanied by alternation of both ventricular chambers simultaneously and synchronously. It is the purpose of this presentation to show, first, that alternation of the pulse pressure in man can occur independently in either the greater or the lesser circulation and, secondly, to demonstrate that the effects of digitalization, leg exercise, and variations in vascular pressures upon pulsus alternans have once more raised questions regarding the mechanisms responsible for this dynamic cyclic event.

Over the past few years, during an investigation of a variety of circulatory abnormalities, pulsus alternans was encountered in 21 patients with cardiovascular disease, although a specific search for this abnormality was not being made. The observations secured in this group form the basis of this paper. The cardiac catheterization technic, utilizing the Fick principle for determination of the cardiac output was employed, and Hamilton manometers or strain-gage pressure transducers with a photo-oscillographic technic* supplied the pressure curves.

Definition of Pulsus Alternans

The cyclic event termed pulsus alternans in this presentation refers to a circulatory state in which there was a regular alternation in pulse pressure, accompanied by a regular rhythm without appreciable variation in cardiac cycle length. The rhythm was of sinus origin in 19 of the 21 cases while atrial flutter and supraventricular tachycardia, probably of A-V nodal origin, were present respectively in each of the remaining 2 cases. It should be emphasized that electric alternans, i.e., change in the size of the electrocardiographic QRS complex, was not present in any of the cases under discussion.

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Presented in part at the Second World Congress of Cardiology and the 27th Annual Scientific Sessions of the American Heart Association, September 13, 1954, Washington, D. C.

* The pressure-recording machine was manufactured by Electronics for Medicine, Inc., White Plains, N. Y.

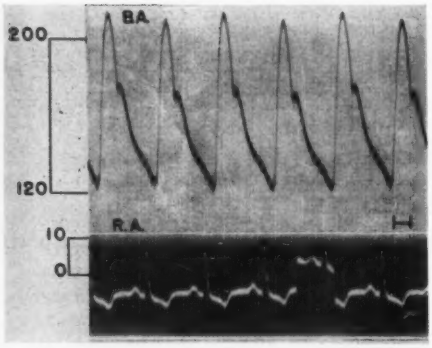

FIG. 1. Pulsus alternans in brachial artery. Pressure curves depicting pulsus alternans in the brachial artery (*B.A.*, upper curve) in patient H.I. no. 345. The right atrial (*R.A.*) curve below the latter shows no alternation. The scale in mm. Hg for each curve appears to the left and standard lead II appears at the bottom of the frame. The maximum systolic difference between the large and small beats in the brachial artery is 5 mm. Hg. These curves were recorded at rest using Hamilton manometers. In this and subsequent figures, unless otherwise noted, the time lines are 0.04 sec. apart and a bar encloses an interval of 0.20 sec.

An example of the classical features of pulsus alternans appears in figure 1, where the brachial artery pressure curve is characterized by an alternately large and small beat.

False Alternans. Instances classed as false alternans were carefully excluded from this study. These are produced either by variation in cardiac cycle length or the effects of breathing, which, respectively, alter diastolic filling time and venous inflow. Some examples of false alternans are found in figures 2 and 3. False alternans can also be produced in the presence of regular rhythm if respiratory and ventricular rates bear a 1:2 or 1:3 relationship to each other.

True Alternans. To return to true pulsus alternans, perhaps the most interesting fact uncovered in this study is the demonstration of the independent alternation of systemic artery or pulmonary artery, a fact previously unknown in clinical medicine. This may be seen in figure 4, where alternation occurs in the brachial artery only, with none in the pulmonary artery or right ventricle. In addition, it is obvious that in this instance alternation occurs in the systolic phase alone, while the diastolic brachial pressure varies only with the respiratory cycle as occurs normally. Figure 5 presents an alternating pulmonary artery; again the variation is apparent only in systole, without evidence of alternans on the systemic side, where there is only a gradual respiratory waxing and waning of the pulse pressure in the femoral artery. It could be argued that diastolic alternation in the pulmonary artery was obscured by the marked effects of respiration upon this pulse contour and, indeed, as can be seen on the left of figure 6, these respiratory effects can almost obliterate even the systolic alternation at times. In the right side of the same figure, recorded when the breath was held, systolic alternans comes out clearly and no diastolic alternans is discernible.

Alternation of pulse pressure in both great vessels is illustrated in figure 7. It is quite obvious that the alternation occurs synchronously in both sides of the circulation, as was true in the other 8 cases with bilateral alternans in this series. These pressures were always recorded simultaneously in contradistinction to the case of DeRabago,[8] where they were not simultaneous, and in whom a nonsynchronous alternation was postulated. In contrast to the previous figures, alternation in figure 7, which was recorded with the breath held, involves both the systolic and diastolic levels in these arteries.

The coexistence of alternation in both circulations is not necessarily fixed, since, as will be seen in the next 3 illustrations, disappearance of pulsus alternans is not necessarily simultaneous in both circuits. In the first illustration (fig. 8), one notes the initiation of bilateral alternans after only 1 premature atrial contraction. Although alternation persists for the 10 beats in the pulmonary artery between the arrows in figure 8, alternans in the brachial artery ceases after the fourth postextrasystolic beat. It is well known that the appearance of variations in size of pulse beats after a premature contraction can persist for 2 or 3 beats after the premature systole on the basis of readjustments in stroke volume. It is difficult to believe that such adjustments would go on for as long as 10 beats. At all events, it would not explain the persistence of alternans in the pulmonary artery when it had ceased in the brachial artery. Figure 9 demonstrates alternans bilaterally in the brachial artery and right

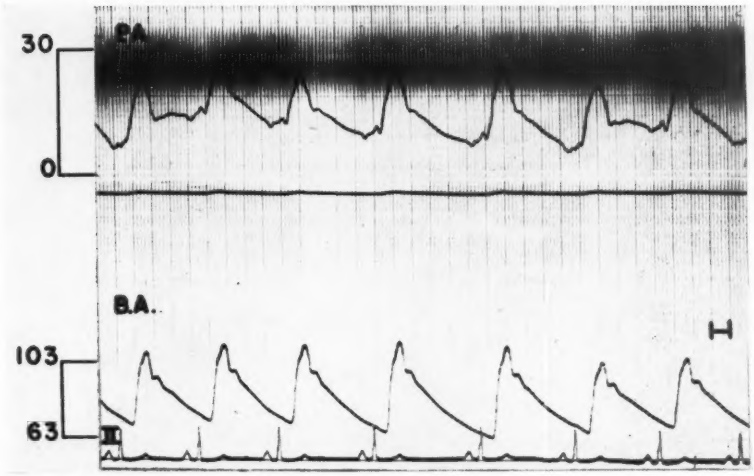

FIG. 2. False alternans during sinus arrhythmia. Pressure curves depicting false alternans in both lesser and greater circulations during sinus arrhythmia (N.G. no. 770). The upper curve is from the pulmonary artery (*P.A.*) and the lower from the brachial artery (*B.A.*), both with scales to the left. Lead II appears at the bottom. These curves, and those in figures 4–7, 11, and 13 were recorded by the use of strain-gage pressure transducers and a photo-oscillographic technic. Note that the pulmonary artery shows the alternating size of the pulse waves more clearly than the brachial artery below it. The diastolic pressure level varies directly with the respiratory cycle, as is the case normally, reaching its peak at full inspiration. The pulse pressure of these beats, however, is related to long and short cycle times as well as to respiratory variations. The second and third pulmonary artery beats have the same cycle lengths but occur during the inspiratory phase, hence the second exceeds the first in height, while the third is waning. The fourth beat, however, occurs after a longer diastole and although from the respiratory pattern it should be declining, it is larger, due to a longer filling time, a greater diastolic volume, and presumably a larger stroke volume. The fifth beat should be the smallest owing to the respiratory influence, but having the longest diastole of all, hence the largest stroke output, it achieves the same size as the fourth beat. The sixth beat with a short diastole occurs at the end of expiration and is again a small one, while with inspiration the seventh beat grows larger despite a short filling period. Here then is a nice balance shown between the influence of respiration on the one hand and cycle length or filling time on the other.

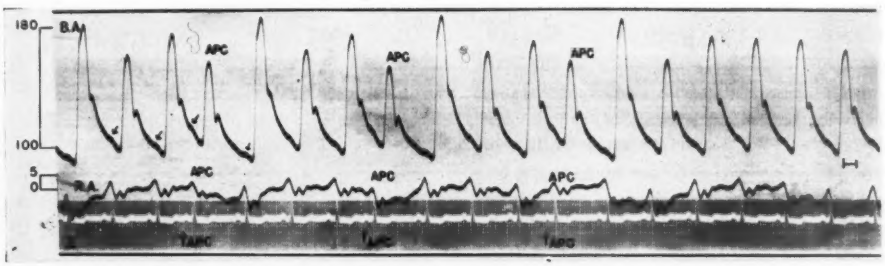

FIG. 3. False alternans in brachial artery due to atrial premature contractions. Pressure curves depicting false alternans in the brachial artery (*B.A.*) due to the regular recurrence of atrial premature contractions (I.J. no. 439). Note the usual small beat in the brachial artery following the premature excitation, the larger postextrasystolic beat and the smaller beat that follows the latter. The timing of the premature atrial contractions is such that, because of variations in diastolic filling and ventricular emptying, a continuous alternation in the brachial artery occurs until the last 5 beats in the figure, where normal sinus rhythm appears uninterrupted by atrial premature systoles. The atrial curve (*R.A.*) shows a mechanical atrial event for each premature beat (*APC*) but no alternation. Lead II is recorded at the bottom of the frame. The series of arrows indicate the registration of the atrial systoles, including 1 premature atrial beat, on the brachial artery curve. Hamilton manometers were used.

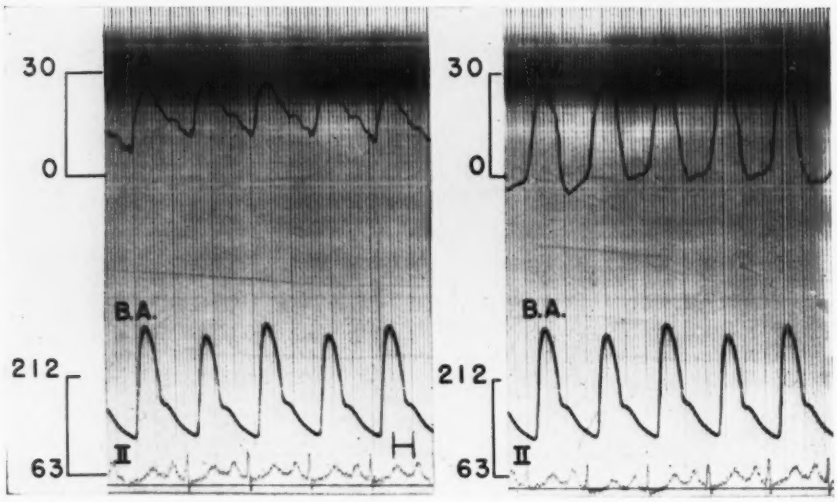

FIG. 4. Pulsus alternans in brachial artery alone. Pressure curves depicting pulsus alternans in the brachial artery alone. This was recorded in the recovery period, 15 min. after exercise was stopped, in patient D.C. no. 778. The upper curves are from the pulmonary artery (*P.A.*) and right ventricle (*R.V.*) and the lower from the brachial artery (*B.A.*) with lead II at the bottom. The maximum systolic difference between large and small beats is 20 mm. Hg. See text for discussion.

ventricle and indicates that after quinidine this latter chamber no longer alternates. The drug produced a fall in right ventricular pressure but effected no change in cardiac output. The cyclic variation in pulse pressure however persists in the brachial artery. Finally, as shown in figure 10, during acute digitalization of a patient in congestive failure with bilateral alternans, the alternate fluctuation in the right ventricle disappears 10 minutes after digoxin was given intravenously, at a time when the cardiac output had risen and the pulmonary artery and right ventricular systolic and diastolic pressures had declined, i.e., when presumably both left and right myocardial performance had been improved. The brachial artery alternans, on the other hand, did not vanish for another 30 minutes. These 3 figures therefore demonstrate the conversion of bilateral into unilateral pulsus alternans. This fact stresses the relatively independent behavior of each of the 2 ventricles and their respective circulations.

The data so far presented have emphasized the existence of unilateral and bilateral pulsus alternans. It has been shown that certain cardiac drugs can obliterate this cyclic dynamic feature in one or the other circulation. Further-

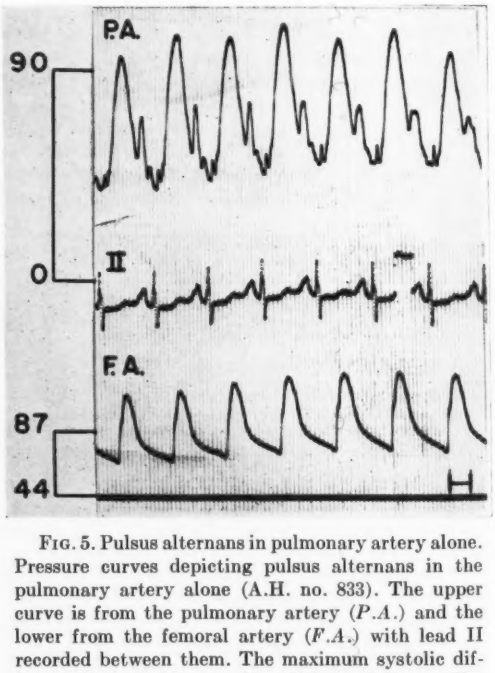

FIG. 5. Pulsus alternans in pulmonary artery alone. Pressure curves depicting pulsus alternans in the pulmonary artery alone (A.H. no. 833). The upper curve is from the pulmonary artery (*P.A.*) and the lower from the femoral artery (*F.A.*) with lead II recorded between them. The maximum systolic difference between large and small beats is 9 mm. Hg. See text for discussion.

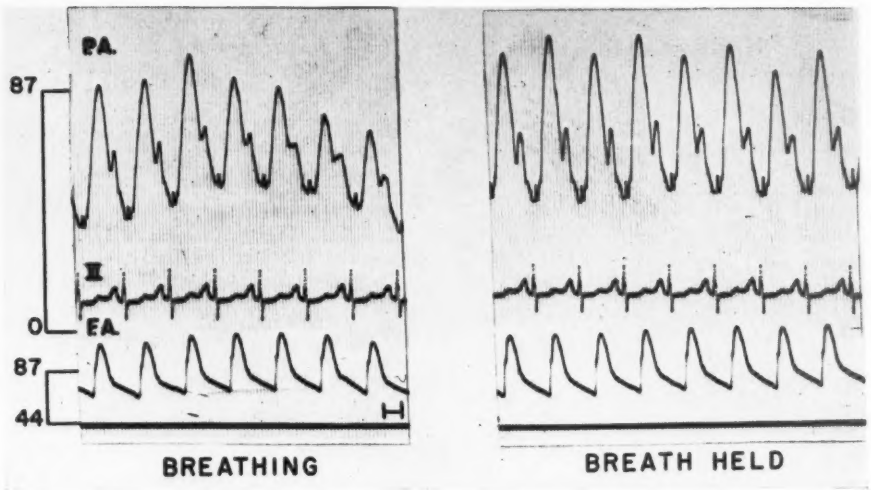

FIG. 6. Pulsus alternans in pulmonary artery. Pressure curves depicting pulsus alternans in the pulmonary artery alone during breathing and with breath held (A.H. no. 833). Curves are from the same patient and are arranged as in figure 5. See text for discussion.

more, a temporary imbalance in the regularity of stroke output as induced by 1 premature systole, was shown to be capable of setting off alternation, a phenomenon that has been described by other investigators.[1, 2] These latter considerations immediately raise the question of the mechanism that may be involved in the production of pulsus alternans. Before considering such mechanisms, certain clinical features associated with pulsus alternans deserve mention.

CLINICAL FEATURES

The relationship between the etiology of the heart disease in these subjects and the presence of unilateral and bilateral pulsus alternans, as well as other related clinical and hemodynamic findings, are of interest and can be seen in table 1. In this series of 21 cardiac patients whose age ranged from 32 to 69 years, 18 must be considered to have advanced heart disease. Three patients (no. 447, 778, 782) however, were minimally, if at all, limited by their disease. Six patients showed alternans on the pulmonary side alone; they suffered from hypertensive or rheumatic heart disease, and 1 had chronic cor pulmonale. Five of these 6 had moderate to severe pulmonary hypertension,

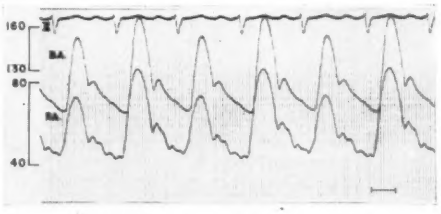

FIG. 7. Pulsus alternans in brachial and pulmonary artery. Pressure curves depicting pulsus alternans in brachial (*B.A.*) and pulmonary arteries (*P.A.*) (B.Y. no. 949). The maximum systolic difference between large and small beats is the same in both arteries, 13 mm. Hg. Lead II appears at the top. See text for discussion.

while in 1, pulmonary artery pressures were normal during alternation. The latter fact suggests that the congested state is not always a necessary accompaniment of pulsus alternans. Six other patients alternated only on the systemic side of the circulation and, of these, 3 were hypertensive while arteriosclerotic or valvular heart disease made up the remainder. Seven of the 9 patients with bilateral alternans had hypertensive or arteriosclerotic disease, or both, and 1 was considered to have idiopathic ventricular hypertrophy, while in the ninth the etiology was unknown. In this last group with bilateral alternans, 8 of the 9 patients were in

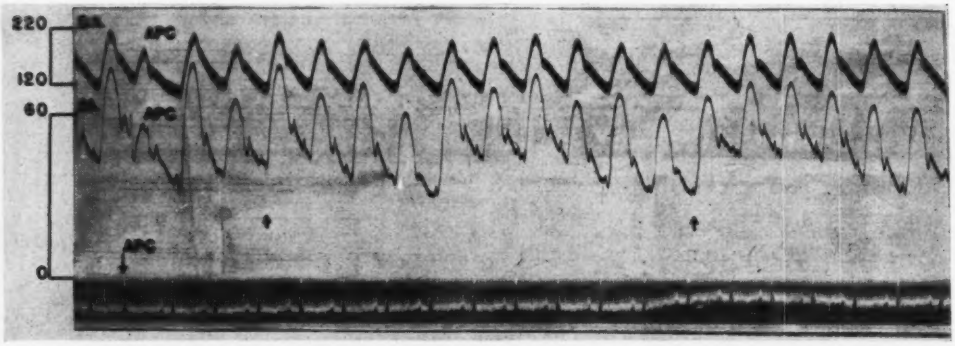

FIG. 8. Pulsus alternans following an atrial premature contraction. Pressure curves depicting pulsus alternans following an atrial premature contraction (*APC*) and recorded with Hamilton manometers (C.G. no. 569). The brachial artery (*B.A.*), pulmonary artery (*P.A.*), and lead II appear from above downward. See text for discussion.

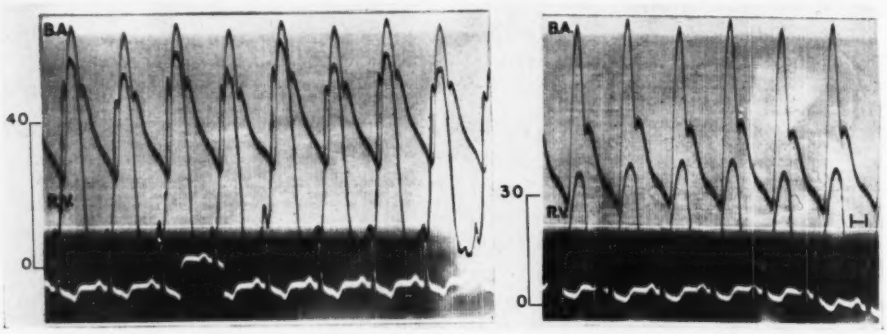

FIG. 9. Disappearance of right ventricular alternans after quinidine. Pressure curves depicting pulsus alternans in both brachial artery (*B.A.*) and right ventricle (*R.V.*) before quinidine (left frame) and its disappearance in the right ventricle (right frame) 35 min. after the drug was given (H.I. no. 345). The electrocardiogram is from lead II. All records were made with Hamilton manometers. See text for discussion.

congestive right and left heart failure with pulmonary and right ventricular hypertension, whereas only one half of each of the groups with unilateral alternans had congestive failure. The degree of alternation on the systemic side varied by as little as 5 and by as much as 30 mm. Hg, while alternating systolic peaks in the lesser circulation differed by 5 to 13 mm. Hg. The cardiac output during alternation in these subjects was either normal or reduced.

A clinical point that has impressed the authors is the almost constant occurrence of an apical diastolic gallop whenever systemic pulsus alternans was found. This relationship was followed by means of a stethogram during the acute digitalization of 1 patient and when the bilateral alternans had disappeared the gallop too had been lost.

The association of intraventricular conduction defects with pulsus alternans is not a close one, since, as can be noted in table 1, bundle-branch block existed in only 3 patients (no. 734, 477, 306). Two (no. 734, 477) had right bundle-branch block and alternated in only the greater or in both circulations. The conduction defect was on the left in the third patient (no. 306) as was the alternans. It was in only this 1 individual (no. 306), who has been described in a previous paper,[10] that the time relationship between the onset of the QRS complex and the onset of the systolic pressure rise in the femoral artery varied, the Q-FA$_s$ time being longer for

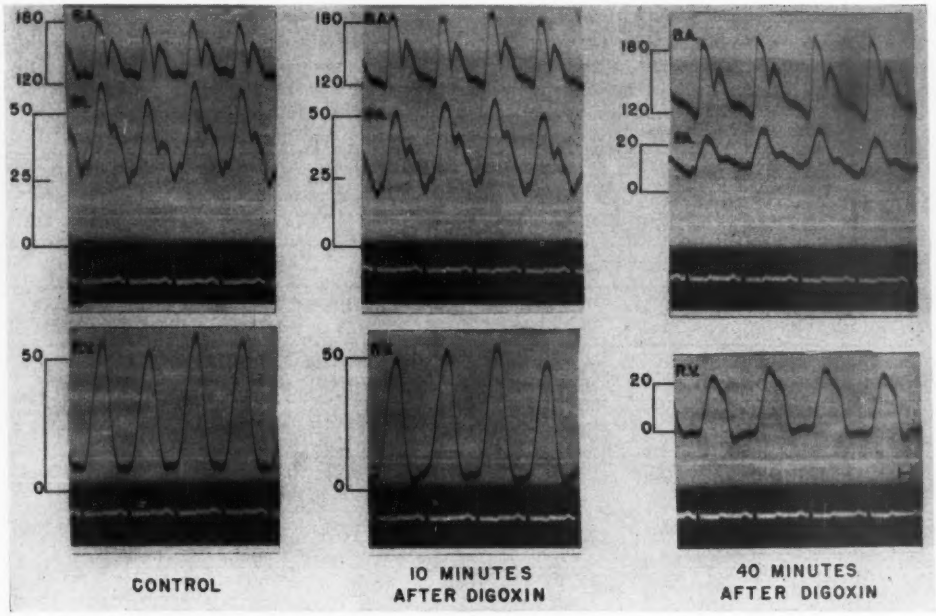

FIG. 10. Disappearance of alternans after digoxin. Pressure curves depicting pulsus alternans which disappeared after digitalization (W.M. no. 616). The upper curve in all 3 frames is from the brachial artery (*B.A.*), the middle the pulmonary artery (*P.A.*), the lower the right ventricle (*R.V.*), while lead II appears in each section. The maximum systolic difference between large and small beats in the control tracings is 7 mm. Hg in both arteries. Hamilton manometers were used to record the pressure pulses. See text for discussion.

the smaller beat. Whether this alternate lengthening of the Q-FA_s time stems from a prolongation of isometric contraction or a decrease in pulse-wave velocity is not known.

DISCUSSION

In considering mechanisms of pulsus alternans, one of the classic concepts that grew out of the animal work on this subject[2] stresses the question of variations in stroke volume. There is no way in which stroke output of each ventricle can be assessed directly in man, but an indication of possible variations in stroke output, if one accepts and applies the Frank-Starling Law, can be had by examination of the diastolic ventricular pressure levels of the individual beats. The pulsus alternans induced in animals has been found to include variations in this diastolic pressure between the small and large beats as well as variations in stroke volume,[2] and it was therefore assumed that this diastolic fluctuation was an integral part of the alternating ventricular systoles.

Examination of the pressure curves obtained in a patient with unilateral right sided pulsus alternans provides information relative to this question of alternation in diastolic pressure levels. Figure 11 contains a right ventricular curve showing ventricular alternans recorded while the patient was holding her breath, a maneuver that minimizes changes in venous inflow as well as variations in pleural pressure, both of which can influence diastolic pressure. It is clear in this figure that only the systolic level alternates, the diastolic pressure remaining at the same level for the large as well as the small beat. Since there is no fluctuation in diastolic filling time as cycle lengths are equal, and no variation in diastolic ventricular pressure, diastolic volume changes must be minimal if present at all. It is also interesting that in none of the patients in this series was alternation found in the right atrial curve.

It is appropriate to note in connection with diastolic filling time, that heart rate was variable in these subjects, and right or left alternans

TABLE 1.—*Clinical and Physiologic Findings in Twenty-one Patients with Pulsus Alternans*

The values given in this table were obtained under resting basal conditions. Unless coupled with a second figure in parentheses, they represent the values obtaining while alternation was present. In four subjects where resting alternans was not present but where alternans appeared in relation to exercise, and in one subject where sudden change in heart rate was associated with alternans, the values during alternation appear in parentheses.

Case, age (yr.), sex	Diagnosis	ECG findings	Cardiac index (L./min./M.² BSA)	Heart rate	Pressures in mm. Hg			TBV (ml./M.² BSA)	PV (ml./M.² BSA)	Hematocrit (%)
					Systemic artery s/d, m	Pulmonary artery s/d, m	Right ventricle s/d			
Alternation in Lesser Circulation Only										
*334, T.C. 49 ♂	CPE, CCP, EH, (G-S), RVF	NST, READ	3.18	110	115/74, 89	—	110/7	4160	1810	57
*609, J.B. 34 ♂	*RHD, EH, MS	NSR, READ, RVH	1.83 (E 1.73)	98 (E 142)	98/68, 85 (E 105/72, 84)	117/61, 87 (E 151/83, 108)	— —	2880	1545	46
*723, F.H. 37 ♂	*RHD, EH, MS, MI, (G-S), CHF	NST, READ, RVH	1.56	107	130/83, 99	86/55, 67	86/15	3171	1583	50
*833, A.H. 39 ♀	RHD, EH, MS	NST, READ, RVH	2.87	115	114/69, 98	93/48, 68	93/3	2094	1149	47
*569, C.G. 57 ♂	HCVD, EH, CHF	NSR, NEAD	2.03	62	208/125, 157	76/44, 60	76/14	4150	1816	55
*739, M.C. 66 ♀	HCVD, ASHD, EH, CS, MF, OMI, CHF	NSR, LEAD, Low voltage, Q_3T_3 pattern	1.62	69	148/71, 102	25/9, 15	25/1	2572	1543	40
Alternation in Greater Circulation Only										
*306, S.H. 57 ♂	HCVD, ASHD, EH, CS, MF, CHF	NSR, LEAD, LBBB with Q_1	2.03	74	196/108, 135	—	33/7	2910	1760	40
*447, E.B. 69 ♀	ASHD, CS, MF	NSR, NEAD	3.85	85	184/82, 118	24/8, 12	24/0	2880	1750	39
*778, D.C. 42 ♀	HCVD, EH	NSR, LEAD (1st. study)	3.62 (E 4.27)	88 (E 120) (R 98)	283/118, 181 (E 317/133, 218) (R 284/129, 195)	37/18, 28 (E 56/26, 39) (R 26/11, 19)	37/4 — (R 26/1)	2636	1342	49
		(2nd. study)	3.24 E 4.38	82 E 132 (R 93)	195/111, 149 E 209/133, 171 (R 180/113, 143)	27/13, 19 E 61/31, 46 (R 23/11, 16)	27/0 E 61/5 (R 23/0)	2863	1498	50
*477, W.W. 56 ♂	ASHD, EH, CS, MF, CHF	Atrial flutter, RBBB	1.85	200	106/81, 87	22/16, 17	22/9	3930	2110	46
*782, L.L. 32 ♀	RHD, EH, MS, MI	NST, NEAD	3.23 E 3.86	110 E 120 (R 110)	126/70, 91 E 143/82, 105 (R 126/76, 93)	18/11, 14 E 32/19, 25 (R 18/11, 14)	18/2 — —	2307	1375	42
*788, J.D. 55 ♂	*CAD, EH, AS, AI	NSR, NEAD	3.25 (E 5.36)	88 (E 132)	135/54, 86 (E 192/85, 129)	20/7, 14 (E 49/29, 39)	20/0 (E 49/7)	3131	2062	36
Alternation in Both Circulations										
*466, G.R. 54 ♂	HCVD, EH, LVF	NST, LEAD	2.20	120	215/144, 166	57/43, 48	57/3	3140	1740	45
*345, H.I. 51 ♂	HCVD, EH, CHF	NST, LEAD	2.77	110	222/130, 162	—	60/9	3200	1775	44
*519, J.M. 38 ♂	HCVD, EH, CHF	NST, LEAD	2.15	111	210/131, 155	57/30, 40	57/11	3340	1940	42

TABLE 1.—*Continued*

Case, age (yr.), sex	Diagnosis	ECG findings	Cardiac index (L./min./ M.² BSA)	Heart rate	Pressures in mm. Hg			TBV (ml./ M.² BSA)	PV (ml./ M.² BSA)	Hematocrit (%)
					Systemic artery s/d, m	Pulmonary artery s/d, m	Right ventricle s/d			
Alternation in Both Circulations—*Continued*										
*616, W.M. 32 ♂	HCVD, EH, CHF	NSR, NEAD	2.56	98	173/123, 140	56/25, 39	56/10	3237	2145	33
*492, M.R. 63 ♂	ASHD, EH, CS, MF	NST, NEAD (Supravent. tachycardia)	— —	103 (136)	125/69, 99 (135/76, 99)	43/13, 28 (25/10, 18)	43/4 —	3250	1925	41
*670, A.S. 67 ♂	ASHD, EH, CS, MF, CHF, CPE	NST, LEAD	—	111	143/82, 102	57/23, 35	57/11	3540	1867	47
*865, A.R. 46 ♂	IVH, EH	NSR, NEAD, LVH	1.94	100	128/85, 102	21/11, 14	—	3540	1770	50
*734, L.K. 63 ♂	UHD, EH, CHF	NSR, READ, RBBB	—	100	110/74, 92	66/34, 47	66/15	—	—	—
*949, B.Y. 60 ♂	HCVD, ASHD, EH, CS, MF, CHF	NST, LEAD	1.79	117	152/95, 116	75/40, 53	75/15	2975	1697	43

* Confirmed by necropsy; AI = aortic insufficiency; AS = aortic stenosis; ASHD = arteriosclerotic heart disease; CAD = calcific aortic disease; CCP = chronic cor pulmonale; CHF = congestive heart failure; CPE = chronic pulmonary emphysema; CS = coronary sclerosis; E = exercise; EH = enlarged heart; (G-S) = Graham-Steell murmur; HCVD = hypertensive cardiovascular disease; IVH = idiopathic ventricular hypertrophy; LBBB = left bundle-branch block; LEAD = left electric axis deviation; LVF = left ventricular failure; LVH = left ventricular hypertrophy; MF = myocardial fibrosis; MI = mitral insufficiency; MS = mitral stenosis; NEAD = no electric axis deviation; NSR = normal sinus rhythm; NST = normal sinus tachycardia; OMI = old myocardial infarct; PV = plasma volume; R = recovery; RBBB = right bundle-branch block; READ = right electric axis deviation; RHD = rheumatic heart disease; RVF = right ventricular failure; RVH = right ventricular hypertrophy; TBV = total blood volume; UHD = unknown heart disease.

was found at ventricular rates between 62 and 200. The appearance or disappearance of this cyclic variation may occur independently of ventricular rate, suggesting that, although rapid heart rates are known to induce pulsus alternans, the mechanisms involved in producing this peculiar cyclic event are not necessarily conditioned by diastolic filling time. These observations raise the question as to whether variations in stroke volume constitute an integral part of pulsus alternans in the lesser circulation.

Besides variation in stroke volume, changes in vascular resistance have been invoked as contributing factors in pulsus alternans.[9] Unfortunately, it is not possible to measure this variable in man under many circumstances. One can, however, determine whether variations in pulmonary and systemic arterial pressures have any influence upon pulsus alternans. Pulmonary circuit alternans, absent at rest, has been seen to appear in association with a rise in pulmonary artery pressure during exercise in 2 rheumatic subjects. This finding is illustrated in figure 12. Similarly, systemic

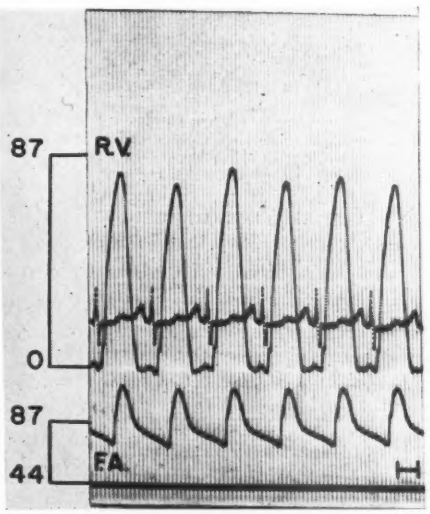

FIG. 11. Right ventricular alternation with breath held. Pressure curves depicting right ventricular (*R.V.*) alternation only and recorded with the breath held (A.H. no. 833). The maximum systolic difference between large and small beats is 6 mm. Hg. The femoral artery (*F.A.*) curve is at the bottom and lead II runs through the right ventricular curve. See text for discussion.

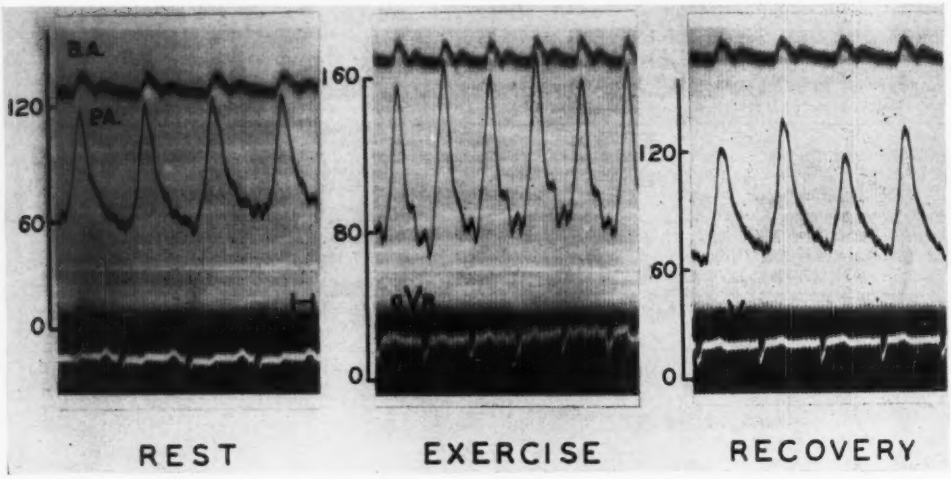

FIG. 12. Pulsus alternans in pulmonary artery. Pressure curves depicting pulsus alternans that appeared in the pulmonary artery (*P.A.*) during exercise and that persisted in recovery (J.B. no. 609). The top curves from the brachial artery (*B.A.*) are too small for accurate analysis as regards alternation. All curves were made with Hamilton manometers. Lead II is recorded at rest and aV_R during exercise and recovery. The maximum systolic difference during alternation in the pulmonary artery on the latter 2 occasions was 13 mm. Hg. See text for discussion.

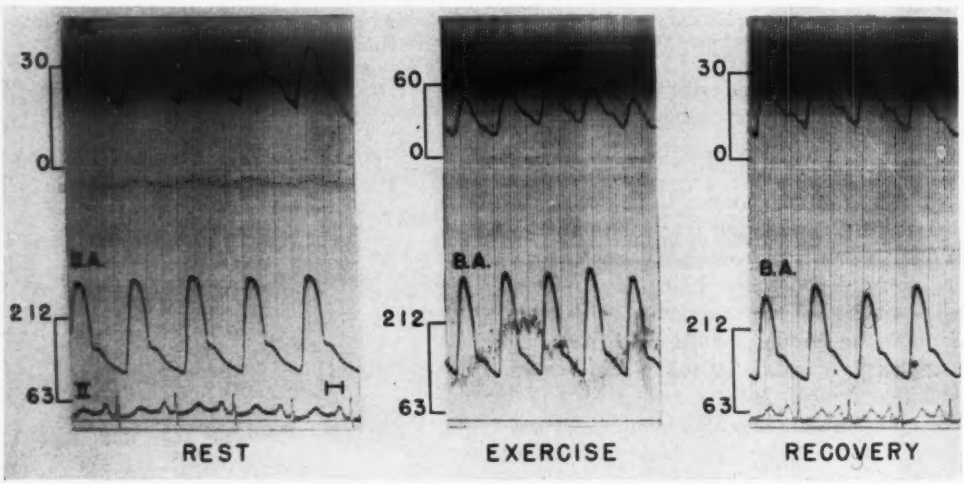

FIG. 13. Pulsus alternans in brachial artery. Pressure curves depicting pulsus alternans which was readily apparent in the brachial artery alone (*B.A.*) in the recovery period, but which could be suspected in the exercise curve (D.C. no. 778). The pulmonary artery (*P.A.*) and lead II also appear in the frames.

alternans was found during exercise (no. 788) at a time when systemic pressures had risen. No alternation appeared, however, in the lesser circuit although pulmonary pressures increased sharply. In another subject (no. 778, first study), systemic alternans, although it began during exercise, became more marked in the recovery period when pressures had fallen (fig. 13). In contrast, systemic alternans has also been noted only in the recovery period in

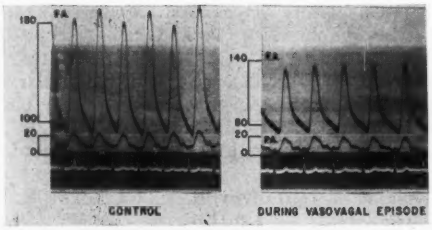

FIG. 14. Disappearance of pulsus alternans in femoral artery after fall in blood pressure. Pressure curves depicting the disappearance of pulsus alternans in the femoral artery (*F.A.*) after a fall in blood pressure, during a vasovagal episode (E.B. no. 447). The pulmonary artery (*P.A.*) and leads II and I also appear in the frames. There is alternation in both the systolic and diastolic pressures in the femoral artery. See text for discussion. Hamilton manometers were used.

2 individuals (no. 778, second study, and no. 782) when pressures that had previously risen during exercise were no higher than at rest. Finally, figure 14 presents a femoral artery alternation that disappeared when this hypertensive patient's blood pressure fell during a vasovagal episode. It is obvious from the widely divergent fluctuations in vascular pressures here described that there is no invariable relationship between changes in pressure and the appearance or disappearance of pulsus alternans. Whether such pressure variations indicate variations in resistance, cannot be stated.

CONCLUSION

The rhythmicity of the phenomenon of pulsus alternans has fascinated physiologists and clinicians for many years and there is still doubt as to its genesis. Wiggers[3] summarizes his views by saying that probably ventricular alternation always involves periodic defections in contractile power of the myocardial fibers, although he admits the possibility of secondary dynamic factors. It is possible that cyclic variations in myocardial contraction can be limited only to those fibers over 1 or the other ventricular chamber in unilateral pulsus alternans. However, if the small beat is really the weaker beat, and this is taken to mean that the small beat delivers the smaller stroke volume, then one would expect, if the Frank-Starling Law applies in these conditions, at least some evidence of alternating end-diastolic ventricular pressure. This has not been found in our patients. Possibly, of course, such pressure changes were too small to be detected in the lesser circulation by present methods in man.

If variable fractionate contractions of the myocardium do not constitute the sole regulating mechanism of this remarkably regular waxing and waning in pulse pressure, one is forced to look for additional and perhaps as yet undiscovered factors. Obviously, variations in pressure and possibly resistance may affect pulsus alternans, but the mechanisms involved are not simple and are probably allied in some fashion with myocardial performance. It may be that there is a resonance phenomenon in the entire ventricular-vascular system by which these alternate systolic amplitudes are initiated and sustained. Be that as it may, unilateral alternans may offer the opportunity in the future of examining in greater detail in man the regulatory factors concerned in producing this interesting phenomenon.

SUMMARY

Studies carried out in 21 patients have indicated that alternation of the pulse pressure in man can occur independently in either the greater or the lesser circulation without appearing in the other. Even when bilateral alternation exists, this cyclic variation may disappear in one circulation while persisting in the other.

Although pulmonary or systemic hypertension was frequently associated with pulmonary and systemic alternans respectively, hypertension was not invariably present. Furthermore, changes in lesser or greater circulation pressures bore no consistent relationship to the appearance or disappearance of pulsus alternans.

Mechanisms responsible for pulsus alternans, in particular variations in stroke volume and vascular pressures, were considered, but no single explanation satisfied the facts revealed in this study.

SUMMARIO IN INTERLINGUA

Studios in 21 patientes ha indicate que alternation del pression pulsatil pote occurrer in homines de maniera independente in o le

circulation major o le circulation minor. Mesmo in casos de alternation bilatere, iste variation cyclic pote disparer in un del circulationes e persister in le altere.

Ben que hypertension pulmonar o systemic esseva frequentemente associate con pulmonar e systemic pulso alternante, respectivemente, le presentia de hypertension non esseva sin exception. In plus, alterationes del pression in le circulationes major e minor non esseva regularmente relationate al apparition o disparition de pulso alternante.

Nulle specific explication del factos revelate in le presente studio se provava satisfactori ben que varie mechanismos responsabile pro pulso alternante esseva prendite in consideration—specialmente variationes del volumine per pulso e del pressiones vascular.

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Medical Eponyms

By Robert W. Buck, M.D.

Tetralogy of Fallot. This syndrome was described by Arthur Fallot (1850–1911) in a "Contribution to the Pathologic Anatomy of the Blue Sickness (Cardiac Cyanosis)" (*Contribution a l'Anatomie pathologique de la Maladie bleue (Cyanose cardiaque)*, which appeared in *Marseille-Médical* 25: 77–93, 138–158, 207–223, 270–286, 341–354, 403–420, 1888.

In his conclusion he says (p. 419):

"The blue sickness, especially when diagnosed in the adult, is the result of a small number of perfectly definite cardiac malformations.

"Of these cardiac malformations, one exceeds all the others in frequency, since we have found it in nearly 74 per cent of our cases. . . .

"This malformation is a true anatomical-pathological entity, represented by the following tetralogy: (1) stenosis of the pulmonary artery, (2) communication between the ventricles, (3) displacement to the right of the origin of the aorta, (4) hypertrophy of the right ventricle, almost always concentric in type. To these may occasionally be added, with only accessory significance, a persistent ductus Botalli."

Status of Fifty Patients Four and a Half to Seven Years after Mitral Commissurotomy

By O. Henry Janton, M.D., Julio C. Davila, M.D., and Robert P. Glover, M.D.

The first 50 consecutive patients undergoing mitral commissurotomy approximately 4½ to 7 years ago have been subjected to a detailed analysis in an attempt to ascertain their present subjective and objective status. Operative mortality was 6 per cent and late mortality was 12 per cent. Forty-one patients (82 per cent) are living and have formed the basis for conclusions. After a comprehensive study of each living patient, including an appraisal of the patient's subjectively reported clinical state, as well as a correlation of the clinical findings, electrocardiographic tracings, teleroentgenograms, and catheterization data, we conclude that 29 patients (71 per cent of those living or 58 per cent of the original 50) are in better condition and living a more nearly normal life than they were prior to surgery.

MITRAL commissurotomy has now become a standard surgical procedure and in recent years a number of reports of the early results have appeared in the literature.[1-6]

This communication presents the clinical, operative, and laboratory findings of 50 consecutive patients in whom mitral commissurotomy was performed between January 1949 and March 1951 and who have been followed for 4½ to 7 years. More than average difficulty was encountered in obtaining all the information for this analysis because these patients live in many parts of the country. Nevertheless, over half of these patients have been examined personally (O.H.J. and R.P.G.), and detailed information including electrocardiograms and teleroentgenograms have been obtained from the patients and attending physicians in the remainder. All patients reported in this series have been operated upon by one surgeon (R.P.G.).

From the Department of Cardiology, Presbyterian Hospital, and Department of Medicine, Hahnemann Medical College and Hospital; the Departments of Thoracic and Cardiac Surgery of Presbyterian and Episcopal Hospitals, and the Department of Thoracic Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pa.

This study was supported by a grant from the American Heart Association.

Presented at the Twenty-eighth Annual Scientific Sessions of the American Heart Association, New Orleans, Louisiana, October 22, 1955.

Case Material

Analysis of Patients

Fifty-one patients were subjected to mitral commissurotomy. One patient was re-evaluated 2 years postoperatively at which time she was asymptomatic without medication; however, at the present time her whereabouts is unknown, and she has not been included in the series. Of the remaining 50, 36 were women, and 14 were men. The average age at the time of surgery was 34 years, the youngest being 17 and the oldest being 47.

Status Prior to Admission. Twenty (40 per cent) patients presented a definite history of rheumatic infection, and each of the 50 patients complained of functional incapacity to some degree. There was a history of gross hemoptysis in 23 patients (46 per cent), and 27 patients (54 per cent) had suffered one or more episodes of congestive heart failure. Six (12 per cent) patients had episodes of arterial embolism from which a reasonable recovery had been made.

Admission Findings. When admitted to the hospital for evaluation for surgery, 13 (26 per cent) of the 50 patients were in chronic congestive heart failure and 19 (38 per cent) were in permanent atrial fibrillation.

Preoperative Classification of Patients. None of the patients was placed in class I according to the criteria of the New York Heart Association[7] (table 1). Five patients (10 per cent) were

TABLE 1.—*Functional Classification*

Preoperative Classes	Postoperative			
	I	II	III	IV
One (0)	0	0	0	0
Two (5)	2	3	0	0
Three (29)	11	11	6	1
Four (7)	1	4	1	1
Total (41)	14	18	7	2

Key: Written numbers designate preoperative functional status; roman numerals designate postoperative functional status; numbers in parentheses designate total number of patients per class preoperatively.

placed in class II, another 36 (72 per cent) were placed in class III, and the remaining 9 (18 per cent) were placed in class IV. Each of these patients was subjected to the standard mitral commissurotomy as described in previous publications.[8, 9]

Mortality. Three patients died within the first postoperative month and represent an operative mortality of 6 per cent. The first died from acute cardiac failure. Postmortem examination revealed a moderately calcified valve of very limited pliability; the previous mitral insufficiency had been increased by the surgery, and a moderately severe but previously undiagnosed aortic stenosis was noted. The second patient died 4 weeks after surgery, the postoperative course being steadily downhill. Postmortem examination revealed that the finger pressure commissurotomy had produced excessive mitral insufficiency, due to an inadvertent tear of the posterior mitral cusp along its lateral attachment. In addition, the superior one third of the left atrial lumen was completely obliterated by a lemon-sized thrombus. The third patient died 2 hours after surgery, apparently due to operative and anesthetic shock, for postmortem examination revealed that a satisfactory commissurotomy had been performed; the only other finding was minimal aortic valve disease.

Six additional patients died, 1 at 6 weeks, 1 at 7 months, 2 at 2½ years, and 2 at 3 years following commissurotomy. These patients had extensively calcified valves whose leaflets were thickened, fibrosed, and nonpliable. Three patients were in class IV and their deaths are attributable to irreversible cardiopulmonary, hepatic, and renal disease at the time of surgery. Three patients were in class III; in 1 of these a pre-existing mitral insufficiency was aggravated by surgery, and the patient went steadily downhill. The remaining 2 patients had inoperable valves that precluded successful commissurotomy.

Thus, there was an operative mortality of 6 per cent (3 patients) and a late mortality within the first 3 postoperative years of 12 per cent (6 patients). Forty-one patients are living at the present time, 4½ to 7 years after surgery, and the data on these patients comprise the remainder of this presentation.

Present Classification of 41 Living Patients. Table 1 shows the classifications. The 5 patients originally placed in class II have lived a relatively normal life since surgery. Two of these patients are asymptomatic and can be placed in class I, and the 3 others have been left in class II, since their fatigue level occasionally is lower than normal.

Thirty of the 36 patients originally placed in class III are living. Eleven of these are asymptomatic and are now in class I. Eleven others have been placed in class II, and 7 remain in class III despite functional improvement. The remaining patient in this group has become more incapacitated and is now in class IV; he is the only patient with progressive incapacity after surgery.

Six of the 9 patients originally placed in class IV are living. One is completely asymptomatic and has been placed in class I, 4 are in class II, and 1 remains in class IV.

The Patient's Classification of His Own Present Status. On close interrogation of the 41 living patients, with confirmation by their family physicians, 20 (40 per cent of the original 50 cases) consider themselves to be in excellent health. They deny symptoms during normal activity, although a few admit to some limitations on exertion beyond their normal routine. These patients engage in exercises such as golf, dancing, swimming, bicycle riding, and bowling. Eleven of these 20 patients take a normal diet and no medication, and 9 take digitalis sporadically in small dosage. Three of these patients were originally placed in class II, 13 in class III, and 4 in class IV.

Sixteen (32 per cent of the original 50 cases) consider themselves very definitely improved over their preoperative state. These patients think that they are living a relatively normal life within their own personal limitations. Thirteen take a daily maintenance dose of digitalis, 3 take no medication, a few remain on a low-salt diet, and 4 use an oral diuretic occasionally. Preoperatively 2 of these patients were placed in class II, 13 in class III, and 1 in class IV.

Five of the 41 living patients (10 per cent of the original 50) regard themselves as unimproved, although each experienced considerable improvement during the first 2 to 4 years postoperatively. Four of these patients were in class III and 1 in class IV prior to surgery.

In comparing our own and the patients' classification of the present status 29 of the 41 living patients (58 per cent of the 50 subjected to surgery) are improved according to us, and 36 (72 per cent of the original 50) are improved according to the patient.

Analysis of Murmurs

Twenty-five of the 41 living patients had "pure" mitral stenosis on the basis of auscultation. Seven of these patients now have no mitral diastolic murmur, and 3 of these 7 have no murmurs at all in any of the valve areas. Three others have a soft, blowing, mitral systolic murmur indicative of some insufficiency, and 1 has an additional soft diastolic murmur along the left sternal border suggestive of aortic insufficiency. Eighteen of the 25 still have a mitral diastolic murmur, and 10 of them have a new mitral systolic murmur.

Ten of the 41 living patients had a systolic component to their predominant mitral diastolic murmurs before operation. Six of them still have their diastolic and systolic murmurs, and 3 others have a systolic murmur only. One patient has no detectable murmurs at this time.

Four of the 41 living patients had a diastolic murmur along the left sternal border suggestive of aortic insufficiency in addition to their mitral diastolic murmurs. In the absence of other clinical signs the aortic insufficiency was thought to be adynamic. Each of these 4 patients still has these murmurs. Two of them have obtained excellent functional results, 1 is markedly improved, and the fourth remains unimproved.

One of the 41 living patients had systolic and diastolic mitral murmurs and an aortic diastolic murmur, and another patient had double murmurs at both areas; these murmurs are still present although the patients are improved functionally.

In conclusion, only 4 of these 41 living patients have no murmurs at the present time. Eleven have no mitral diastolic murmur, and 14 have mitral systolic murmurs of varying intensity that were not present preoperatively.

From a functional standpoint the 25 patients with diagnoses of "pure" mitral stenosis have had the best results. Fourteen are now excellent, 9 are improved, and 2 are unimproved. This improvement is better than in the 10 patients who had predominant mitral stenosis with an associated insufficiency. Of these 10, 4 obtained an excellent result, 4 were improved, and 2 were unimproved.

Electrocardiographic Changes

Rhythm. Twenty-nine patients had normal sinus rhythm at the time of surgery. Atrial fibrillation frequently appeared in this group during the early postoperative course, usually within the first 4 days. In 9 patients, fibrillation persisted despite intensive quinidine therapy during the hospital stay or on occasion thereafter. All of these patients, however, have remained improved or in excellent functional state to the present time.

Twelve patients had atrial fibrillation at the time of surgery, and it persisted. Of these 12, 5 are unimproved, and 7 are improved to excellent.

The P Wave. The P waves generally did not change in duration or configuration. Occasionally, high voltage of the P wave, usually noted in cases with marked pulmonary artery hypertension, was reduced in amplitude after an adequate mitral commissurotomy.

The QRS Complex. Ten patients had normal QRS complexes preoperatively. There were no changes after commissurotomy except for slight counterclockwise rotation around the longitudinal axis.

The remaining 31 patients had preoperative

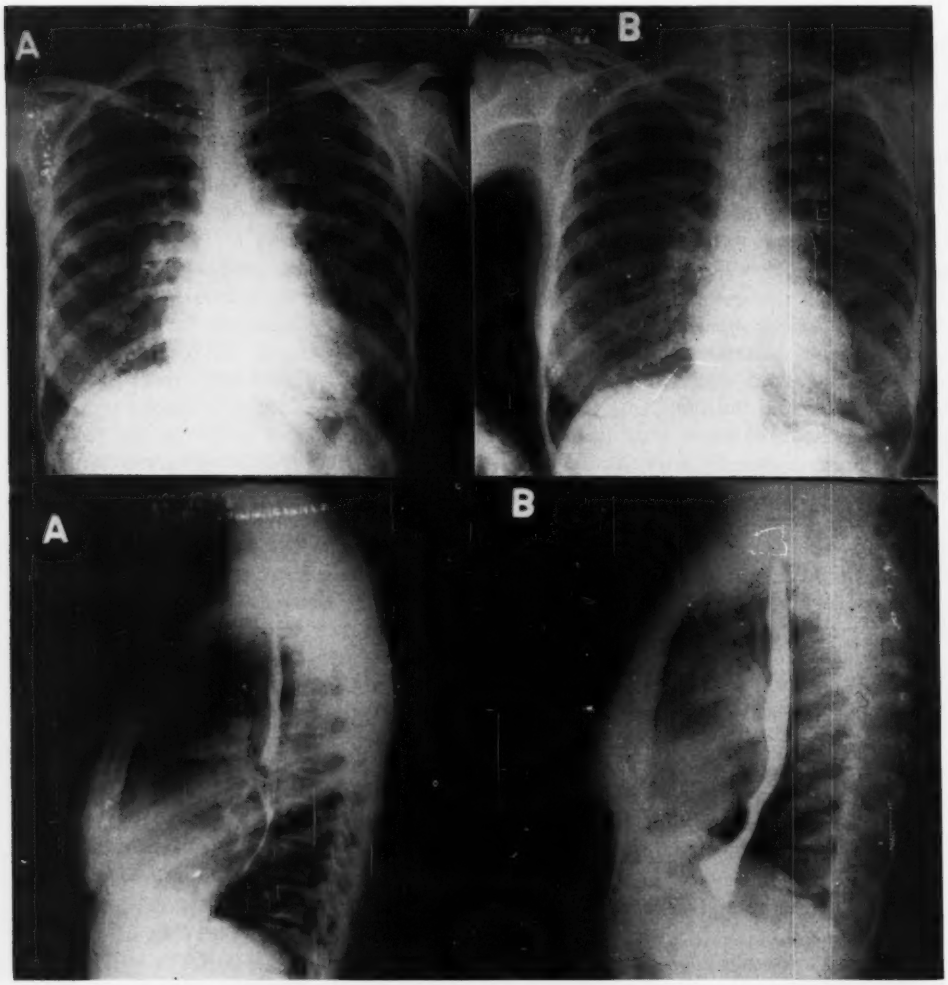

FIG. 1. V.S. Commissurotomy June 27, 1949. *A*. June 21, 1949. *B*. Feb. 15, 1954. Postoperative decrease in the cardiac silhouette, as noted in 10 patients (24 per cent).

electrocardiograms indicative of moderate to marked right ventricular hypertrophy. This pattern showed a variety of changes postoperatively. It receded in 11 and disappeared in 7. In 13 patients the pattern of right ventricular hypertrophy did not change, except for development of combined hypertrophy in 1. In this individual a dynamic mitral insufficiency is now present.

Roentgenographic Findings. It is frequently rather difficult to evaluate the observed changes in cardiac size because of the many postoperative variables such as pleural reaction, pericardial reaction and adhesions, changes in weight, and the variations in x-ray technic.[10] Despite these difficulties the following statements can be made with confidence.

In 10 patients (24 per cent) the over-all heart size was smaller postoperatively as a result of diminution in size of the right ventricle, pulmonary artery, left atrium, and appendage. As would be expected, 9 of these patients have obtained an excellent result, and the tenth is considerably improved (fig. 1).

In 5 patients (13 per cent) the over-all size of the heart appeared larger, due mostly to an increased size in the left ventricle and perhaps the left atrium. Rather paradoxically perhaps, 4 of these patients consider themselves functionally improved, and 1 is unimproved (fig. 2).

In the largest group, 26 patients (63 per cent), any change in heart size is controversial. In our opinion the cardiac silhouettes remain unchanged (fig. 3).

The implication of these findings is most significant. In the years immediately preceding surgery all these patients showed progressive cardiac enlargement, and now 87 per cent have a cardiac silhouette either the same size or smaller. This is strong objective evidence of favorable clinical response to mitral commissurotomy.

Cardiac Catheterization Data (*table 2*). The preoperative studies were made 4½ to 7 years ago and are limited according to present standards. Nevertheless, all data are presented. Twenty-three of the 27 patients in whom data are available have obtained sig-

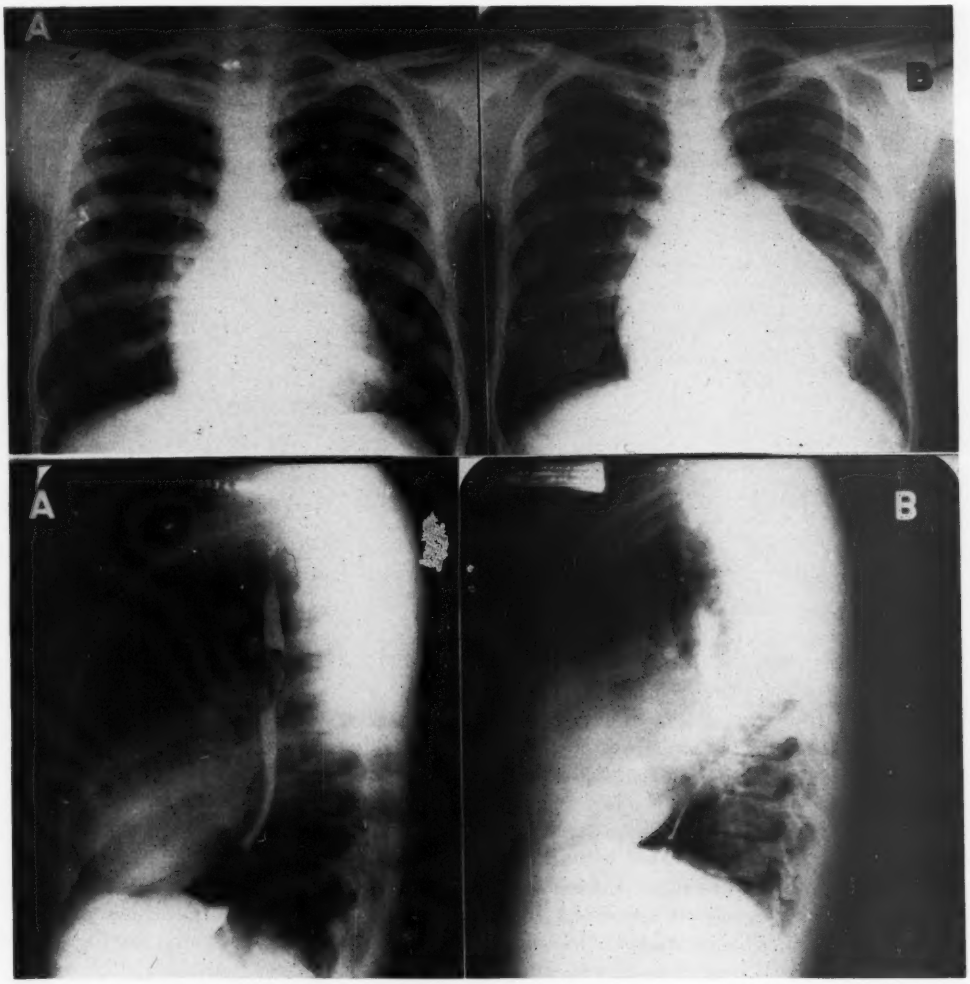

FIG. 2. J.K. Commissurotomy Nov. 23, 1949. *A*. Nov. 14, 1949. *B*. Mar. 9, 1954. Postoperative increase in the cardiac silhouette as noted in 5 patients (13 per cent).

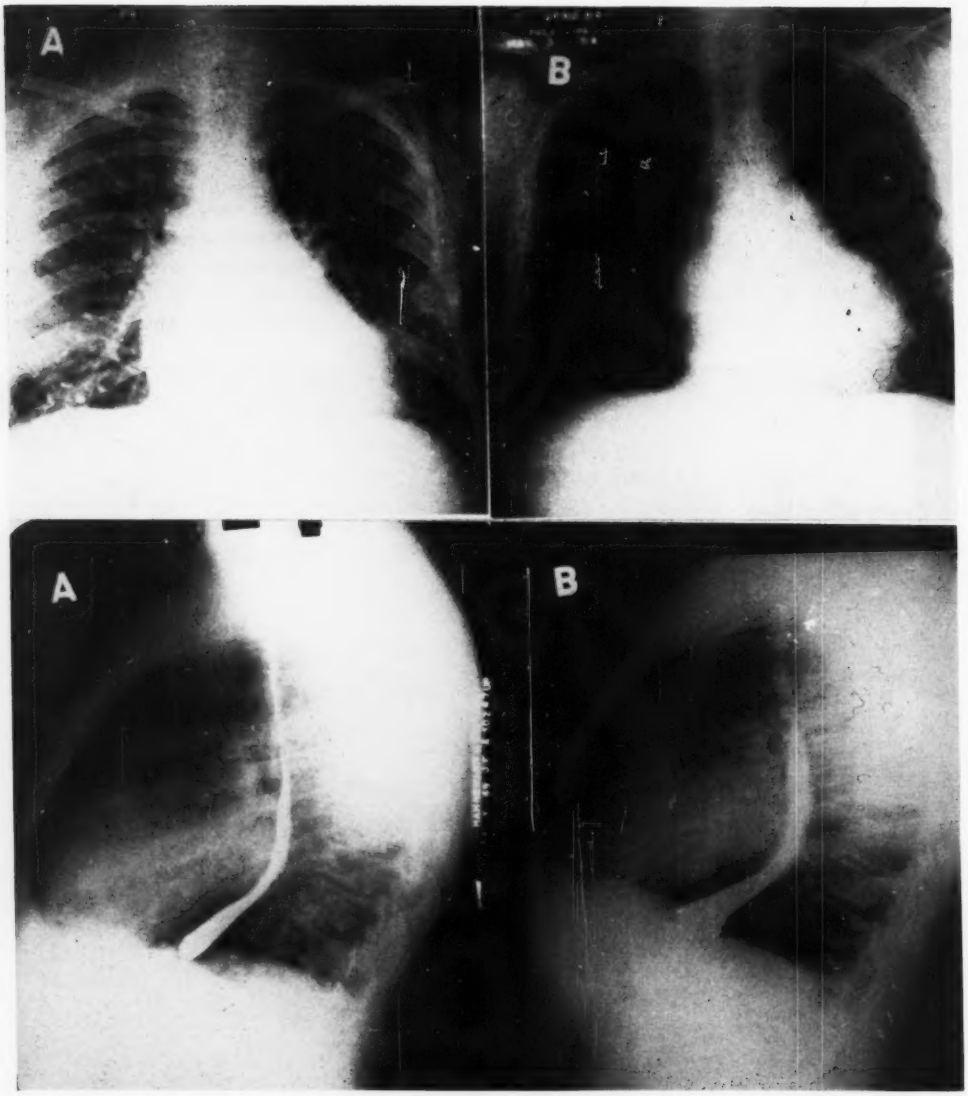

FIG. 3. T.S. Commissurotomy Nov. 7, 1949. *A*. Nov. 1, 1949. *B*. Mar. 3, 1954. No significant postoperative change in the cardiac silhouette, as noted in 26 patients (63 per cent).

nificant and sustained functional improvement. In all but 2 the reduced pressure within the pulmonary vascular bed and right ventricle has paralleled and objectively corroborated the clinical improvement. These 2 patients (no. 11, H.E., and no. 12, R.B.) are in excellent status now, but the pressure dropped slightly in one and rose in the other. Since the catheterizations in these patients were carried out only 1 month after surgery, perhaps the circulation had not yet readjusted to final levels.

In the 4 patients who remained unimproved after surgery, only 2 were catheterized during the postoperative period, but neither of these showed a significant pressure drop, again a good agreement with the observed clinical state.

Valvular Findings. In tight mitral stenosis,

TABLE 2.—*Available Catheterization Data*
27 of 41 Living Patients

Case	Pre-operative		Postoperative		Months	Clinical Results
	Rt. Vent.	Pul. Art.	Rt. Vent.	Pul. Art.		
1. J.B.	90/17 (41)*	—	48/3 (18)	—	20	Excellent
2. E.W.	82/2	84/38	56/1	63/19	1	Unimproved
3. V.S.	141/5 (50)	143/56 (85)	33/14 (20)	36/15 (22)	15	Excellent
4. T.S.	43/3 (16)	42/12 (22)	27/5 (12)	—	33	Excellent
5. J.K.	60/4	81/31	23/8	24/6	65	Improved
6. S.G.	42/?	55/7	7/4	—	1	Improved
7. E.M.	55/36 (42)	49/30 (36)	28/0 (9)	35/10 (18)	13	Improved
8. V.C.	100/9 (39)	130/59 (83)	26/5 (12)	24/8 (13)	21	Excellent
9. G.K.	50/2 (18)	48/24 (32)	47/4 (18)	52/23 (33)	10	Unimproved
10. W.F.	25/−1	24/11	—	—	—	Unimproved
11. H.E.	66/3	54/27	48/8	48/21	1	Excellent
12. R.B.	36/1	31/15	54/4	—	1	Excellent
13. G.D.	89/0	87/39	50/−2	50/18	9	Improved
14. F.L.	68/0 (23)	—	52/2 (21)	—	16	Excellent
15. H.D.	72/5	78/42	—	—	—	Improved
16. C.W.	37/4	32/14	—	—	—	Unimproved
17. A.N.	(37)	(72)	(2)	(14)	61	Improved
18. M.S.	43/3	48/18	—	—	—	Improved
19. E.C.	64/−3(25)	75/27 (43)	30/0 (10)	30/10 (17)	14	Excellent
20. J.A.	—	57/44	24/30	38/18	12	Excellent
21. E.I.	93/6 (35)	105/24 (51)	24/−6(7)	23/4 (14)	61	Excellent
22. A.G.	59/−7	59/17	—	—	—	Improved
23. M.Q.	21/7	36/−3	—	—	—	Excellent
24. M.D.	32/−2	30/16	20/8	20/6	14	Excellent
25. H.O.	67/0	68/29	—	—	—	Improved
26. M.J.	78/5	82/35	—	—	—	Excellent
27. I.J.	53/0	63/26	48/0	36/15	1	Improved

* Figures in parentheses refer to mean pressures

with an orifice the size of a cigarette or less, the more pliable the valve, the better the result.

Twenty (49 per cent) patients had some degree of valvular calcification. Seventeen remained definitely improved, but only 6 can be considered excellent. Twenty-one patients (51 per cent) had no evidence of valvular calcification, and 18 remain considerably improved; however, 14 of the 18 are in excellent condition, and represent a decidedly better result than the group with calcification.

Three patients with densely fibrotic valves but no detectable calcium were essentially unimproved after surgery.

Reactivation of the Rheumatic State. Rheumatic activity is difficult to determine in patients who do not show the full-blown syndrome of rheumatic fever. However, one of us (O.H.J.) was the first to call attention to the possible reactivation of the rheumatic state following mitral commissurotomy and termed it "pleuropericarditis."[2, 11] Eight (19.5 per cent) of these 41 living patients have had repeated postoperative episodes of cyclic fever, painful swollen joints, tachycardia, pulmonary and peripheral congestion, and thoracic or precordial pain, which certainly might be regarded as rheumatic activity. In only 3 of the 8 patients with postoperative rheumatic activity were there rheumatic changes in the biopsied left auricles. Thirteen other atrial appendages of these 41 living patients likewise showed rheumatic stigmata, but the patients showed no clinical evidence of rheumatic activity.

Thromboembolic Data. Despite the facts that the left atrium was traversed in each instance, that 7 were obliterated by thrombotic material, and that approximately half the valves contained calcium, only 1 embolus occurred during operation. A complete left hemiplegia resulted from which the patient has recovered except for

the finer motions of the left hand; clinically this patient has obtained an excellent result. In contrast, the over-all incidence of emboli in our first 500 consecutive mitral commissurotomies was 4.4 per cent, of which 2.6 per cent were cerebral and 1.8 per cent were peripheral.[4] There have been no embolic episodes during the postcommissurotomy period.

Miscellaneous Postcommissurotomy Medical Events. Several patients have undergone unrelated surgery and other medical events without complication or deterioration of their cardiac status. Four patients had a total of 5 normal pregnancies and deliveries.[12] Other events include 2 cholecystectomies; 2 appendectomies, 1 for a ruptured appendix; 1 hysterectomy, 1 myomectomy, and 3 curettages of the uterus; 1 hemorrhoidectomy; and 1 rather severe myocardial infarct with recovery.

Summary

The first 50 consecutive patients who underwent mitral commissurotomy approximately 4½ to 7 years ago have been subjected to a detailed analysis of their present subjective and objective status. None of these patients was in class I, 5 (10 per cent) were in class II, 36 (72 per cent) were in class III, and 9 (18 per cent) were in class IV. Operative mortality was 6 per cent (3 patients), and late mortality was 12 per cent (6 patients), occurring 6 weeks to 3 years postoperatively. Forty-one patients (82 per cent) are living and form the basis for the following.

We conclude that 29 patients (71 per cent of those living or 58 per cent of the original 50) are in better condition and living a more nearly normal life than they were prior to surgery.

According to the 41 living patients and their family physicians, 36 (88 per cent of those living, or 72 per cent of the original 50) are better than they were prior to surgery.

No definitive conclusion can be reached regarding the present clinical status of these patients on the basis of their murmurs alone. Four of the 41 living patients have no murmurs. Eleven do not have their original mitral diastolic murmur. Fourteen have a mitral systolic murmur of varying degrees that was not present preoperatively. Those patients with "pure" mitral stenosis obtain the best results from mitral commissurotomy.

Although the electrocardiographic changes following surgery do not regularly show conclusive evidence of improvement, a small group does show postoperative regression of right ventricular hypertrophy.

By fluoroscopic and teleroentgenographic study, 10 (24 per cent) of the 41 living patients have a smaller cardiac silhouette, 26 (63 per cent) have a silhouette of the same size as preoperatively, and 5 (13 per cent) have a larger cardiac silhouette. In 87 per cent of these living patients the heart is the same size or smaller than prior to surgery, whereas in the years preceding surgery it grew progressively larger.

The available cardiac catheterization data parallel and corroborate the observed functional state of the patient.

Twenty patients (49 per cent) with valvular calcification have not been so greatly improved as 21 patients (51 per cent) without calcification.

Evidence of rheumatic activity was observed during the postoperative period in 8 patients (19.5 per cent).

Valvular restenosis has not been observed in the 41 living patients nor in those who died in the postoperative period.

Only 1 operative embolus was produced in 50 patients, and that patient has recovered almost completely. There have been no postoperative emboli, although the incidence prior to surgery was 12 per cent.

This analysis establishes that commissurotomy confers a genuine, often dramatic, and usually persistent benefit to the patient. It confirms the original hope that this procedure would become a valuable adjunct in the overall treatment of mitral stenosis.

Summario in Interlingua

Le prime 50 patientes consecutive subjicite a commissurotomia mitral a periodos de inter circa 4½ e 7 annos retro esseva includite in le hic presentate detaliate analyse de lor currente stato subjective e objective. Nulle de iste

patientes esseva in classe I; 5 (10 pro cento) esseva in classe II; 36 (72 pro cento) esseva in classe III; e 9 (19 pro cento) esseva in classe IV. Le mortalitate operatori esseva 6 pro cento (3 patientes), e mortes retardate amontava a 12 pro cento (6 patientes) con occurrentias a inter 6 septimanas e 3 annos post le operation. Quaranta-un patientes vive e forma le base del sequente remarcas.

Vinto-nove patientes (71 pro cento del superviventes e 58 pro cento del total original) es meliorate e vive un vita plus normal que ante le intervention chirurgic.

In le opinion del 41 superviventes mesme e etiam in le opinion de lor medicos private, 36 (88 pro cento del superviventes e 72 pro cento del total original) es meliorate in comparation con lor stato ante le intervention chirurgic.

Il non es possible formular conclusiones definitive in re le presente stato clinic de iste patientes super le base de solmente lor murmures. Quatro del 41 superviventes ha nulle murmures. Dece-un non ha lor original murmure diastolic mitral. Dece-quatro ha varie grados de murmure systolic mitral que non esseva presente ante le operation. Le patientes con "pur" stenosis mitral profita le plus ab commissurotomia mitral.

Ben que le alterationes electrocardiographic postoperatori non exhibi uniformemente signos conclusive de melioration, un parve gruppo de patientes revela in lor electrocardiogrammas postoperatori un regression del hypertrophia dextero-ventricular.

Secundo studios fluoroscopic e teleroentgenographic, 10 (24 pro cento) del 41 superviventes ha reducite silhouettes cardiac; 26 (63 pro cento) ha silhouettes del mesme dimensiones como ante le operation; e 5 (13 pro cento) ha silhouettes allargate. In 87 pro cento del superviventes le corde ha le mesme dimensiones como ante le operation o es devenite plus parve, durante que in le curso del annos precedente le chirurgia illo cresceva progressivemente.

Le disponible datos catheterisational corrobora le observate stato functional del patiente.

Vinti patientes (49 pro cento) con calcification valvular se ha meliorate minus que 21 patientes (51 pro cento) sin calcification valvular.

Signos de activitate rheumatic esseva observate postoperatorimente in 8 patientes (19,5 pro cento).

Re-stenosis valvular esseva observate in nulle del 41 superviventes e in nulle del patientes qui moriva post le operation.

Solmente un embolo operative esseva producite in le integre serie de 50 patientes. Le individuo in question ha recovrate quasi completemente. Nulle embolos ha occurrite postoperatorimente, ben que le frequentia ante le operation amontava a 12 pro cento.

Le presente analyse prova que commissurotomia representa pro le patiente un beneficio genuin que es frequentemente frappante e generalmente persistente. Le analyse justifica le spero original que iste technica devenirea un adjuncto importante in le tractamento general de stenosis mitral.

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WILLIAM WITHERING

William Withering (1741–1799) a graduate of Edinburgh was the discoverer of the therapeutic virtues of digitalis. One of the ablest English clinicians, he published various clinical treatises including "An Account of the Scarlet Fever and Sore Throat or Scarlatina Anginosa, Particularly As It Appeared at Birmingham in the Year 1778." A physician with broad interests, he determined the chemical composition of minerals and mineral waters, was a breeder of cattle and dogs, a climatologist, and engaged in playing the flute, bag pipes and harpsichord. During his medical student days, he disliked the study of botany, but having fallen in love with Helena Cooke, a young amateur painter of flowers, who subsequently became Mrs. Withering, his interest in plants and flowers grew apace. His five volume masterpiece "The English Linnaeus" established his fame as one of the greatest of medical botanists. His knowledge of botany and the pharmacological properties of various plants was, indeed, largely responsible for his great discovery. As Withering states on the second page of the Introduction in his great classic ("An Account of the Foxglove and Some of Its Medical Uses"—Birmingham 1785.):

"In the year 1775, my opinion was asked concerning a family receipt for the cure of the dropsy. I was told that it had long been kept a secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed. I was informed also, that the effects produced were violent vomiting and purging; for the diuretic effects seemed to have been overlooked. This medicine was composed of twenty or more different herbs; but it was not very difficult for one conversant in these subjects, to perceive, that the active herb could be no other than the Foxglove."

His last years were clouded with recurrent attacks of "consumption" and finally led to his death in 1799 when he was 58 years of age. A friend who visited him during his last days was responsible for the celebrated pun, uttered sadly and with warm affection, "The flower of English physicians is indeed 'withering.' "—ED.

Arteriovenous Fistula of the Renal Vessels

A Case Report

By JON R. MYHRE

Hematuria presents an urgent problem in differential diagnosis. A patient was observed with hematuria for renal colic with characteristic radiation in whom an arteriovenous fistula due to vascular erosion by adenocarcinoma of the kidney was found. This condition has been reported only rarely. Previous reports of this condition are reviewed and the findings discussed.

UP TO 1953 only 4 proved cases of arteriovenous fistula of the renal vessels had been reported.[1] An additional case is described here, in which aortography also revealed small shunts in the liver and the pulmonary artery; the involved renal vein and the hepatic vein were catheterized.

CASE HISTORY

A 66-year-old woman was admitted to the hospital in October 1955, suffering from hematuria that had started a few hours earlier. Previously she had enjoyed good health. The hematuria was followed by severe right renal colic with typical localization and radiation of the pain.

The height was 161 cm., the weight 51.7 Kg., the blood pressure 140/70 mm. Hg. There were no signs of cardiac enlargement. A grade II systolic murmur was heard at the apex. In the right hypochondrium there was a definite systolic-diastolic thrill and murmur. The values for hemoglobin, red blood cell count, and blood urea were normal. Massive hematuria was found.

Because of the murmur and thrill, an arteriovenous fistula of the renal vessels was assumed to be present.

After a few days the pain gradually disappeared, and after a week no trace of blood could be found in the urine.

An x-ray film of the chest gave no indications of augmented pulmonary circulation. The cardiac shape and size (350 ml./sq.M. by the formula of Jonsell[2]) were normal. The electrocardiograms were also normal. The cardiac output (from catheterization data of the pulmonary artery and the Fick principle) was somewhat high, being 7.1 and 7.6 L./min. on 2 subsequent determinations, and the mean cardiac index was 4.8. The arteriovenous oxygen difference was 34 ml./min./L. The pressures in the pulmonary artery were 27/10 mm. Hg, with a mean of 15 mm. Hg, slightly higher than usual; the zero position was taken as 10 cm. above the dorsal surface. The blood volume determined with Evans blue was normal, 2.5 L./sq.M.

The glomerular filtration rate (inulin) and the renal plasma flow (para-aminohippuric acid) were respectively 79 ml./min. and 363 ml./min., when corrected for a body surface area of 1.73 sq.M. The concentration test of Addis and Shevky resulted in a urinary specific gravity of 1.024.

Urography showed delayed and reduced excretion from the right kidney and a distortion of the renal pelvis, indicating an expanding hilar process (fig. 1). Transfemoral aortography revealed a large arteriovenous communication of the renal vessels on the right side and also some smaller shunts in the liver (fig. 2). Catheterization of the liver veins did not, however, show a high oxygen content in 2 blood samples from these vessels, the saturation being respectively 66 and 67 per cent in 2 different positions in the right lobe of the liver. The first position was not far from one of the shunts, as judged from the frontal view, while the second position was more centrally placed. Catheterization of the right renal vein revealed an abnormally high oxygen content in the blood samples, the saturation being respectively 90, 94, and 94 per cent in blood from 3 different positions. The first result was derived from the most lateral position. The oxygen saturation in samples from the femoral artery was 96 per cent. The pressures registered in the right renal vein were not higher than usual (systolic 7, diastolic 2, mean 4 mm. Hg), and the pressure gradient between the renal vein and the inferior caval vein was not appreciably raised.

Surgical intervention was discussed. Since the patient did not wish any operation except as a last resort, and since the finding of multiple aneurysms suggested a congenital condition, it was decided to avoid surgical treatment unless recurring hematuria or evidence of overloading of the heart should necessitate it. She left the hospital after a stay of 4 weeks, feeling completely well. On control examination 10 weeks later, the urine was normal, and the size and shape of the heart were unchanged.

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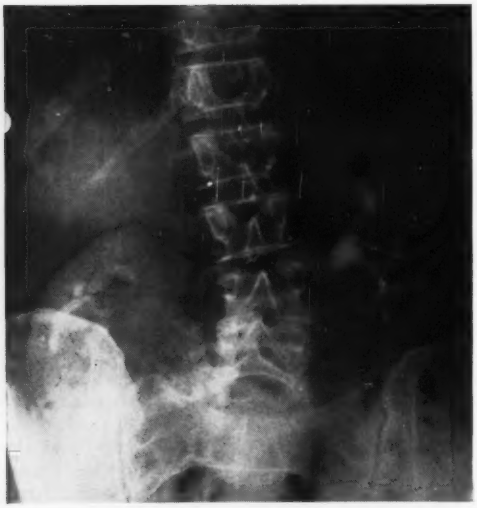

FIG. 1. Urogram showing a reduced excretion of the right kidney and distortion of the right renal pelvis.

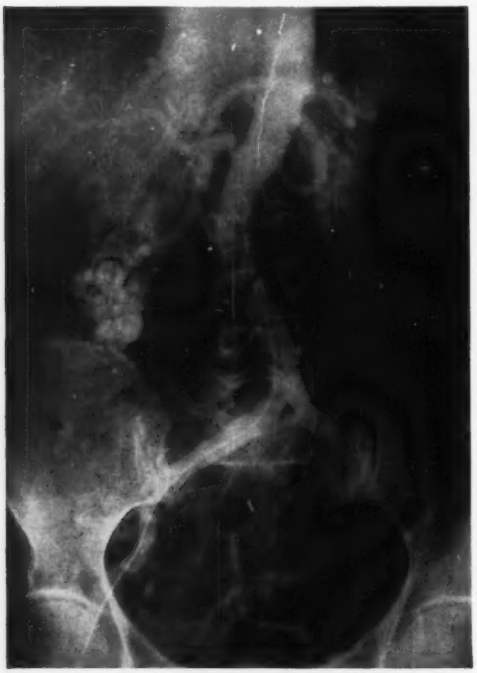

FIG. 2. Aortogram. Transfemoral method. The hepatic, splenic, and superior mesenteric arteries, both renal arteries, the large arteriovenous communication in the right kidney, and the smaller shunts in the liver.

Hematuria recurred in April 1956 and the kidney was removed. In it was found an adenocarcinoma, which partly surrounded the grossly dilated hilar veins and produced a communication by erosion between these vessels and a branch of the renal artery. Tumor tissue protruded as a solid mass far into the dilated renal vein. There were no congenital vascular abnormalities. The vascular abnormalities demonstrated in the liver were then considered to be incidental, unrelated lesions, most likely hemangiomas.

DISCUSSION

It is believed that 3 of the earlier reported cases[3-5] of arteriovenous fistula of the renal vessels were due to congenital aneurysms; in the fourth case,[1] a neoplastic erosion of the vessels had taken place. Most recently 2 additional cases of arteriovenous fistula of the renal vessels have been reported.[6, 7] In 1 of these cases, a traumatic fistula in a 6-year-old girl, a blood pressure of 146/110 mm. Hg was registered. In the other case, which probably was of congenital origin, the blood pressure was 150/60. Garritano and associates have also traced still another case in the literature in which, however, the blood pressure values or other clinical data were not reported.[8]

It has been maintained that the arteriovenous fistula of the renal vessels holds a unique position in being the only such communication causing hypertension. Neither the case of Pearse and MacMillan[3] nor our case, however, was hypertensive, and in one of the remaining cases the blood pressure was only 160/80 mm. Hg.[5] The blood pressure in the case of Hamilton, Getz, and Jerome[1] was 170–168/100–92 mm. Hg, and before hospitalization a blood pressure of 180/110 had been recorded. This is certainly a noteworthy finding in a case of arteriovenous shunt, especially since the age of the patient was only 29 years. A more severe hypertension, 220/120 mm. Hg, has been found only in the case of Rieder.[5]

Absence of definite enlargement of the heart in our case tallies well with the fact that the size of the heart may sometimes remain normal into old age in cases of persistent ductus arteriosus with a similar moderate degree of shunting.

SUMMARY

A case of arteriovenous fistula of the right renal vessels in a 66-year-old woman is de-

scribed. The right kidney was removed after recurrent hematuria and adenocarcinoma was found, which produced the arteriovenous fistula by erosion of the vessels. The blood pressure was 140/70 mm. Hg; the size of the heart was normal, but the output was high, with a cardiac index of 4.8. The oxygen saturation in blood samples from the right renal vein varied from 90 to 94 per cent.

Aortography demonstrated the shunt well and also revealed smaller shunts in the liver, but the oxygen saturation in blood samples from the liver veins was not higher than normally found.

Summario in Interlingua

Es describite un caso de fistula arteriovenose del vasos dexterorenal in un femina de 66 annos. Le ren dextere esseva abferite post recurrente hematuria; e adenocarcinoma esseva trovate le qual produceve le fistula arterio-venose per erosion del vasos. Le pression sanguinee esseva 140/70 mm Hg. Le corde esseva de dimensiones normal, sed le rendimento esseva alte: le indice cardiac esseva 4,8. Le saturation oxygenic in specimens de sanguine ab le vena dexterorenal variava ab 90 a 94 pro cento.

Le shunt esseva aortographicamente ben demonstrabile. Le examine aortographic etiam revelava plure shunts de extension minor in le hepate, sed le saturation oxygenic in specimens de sanguine ab le venas hepatic non excedeva constatationes normal.

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Zoll, P. M., Linenthal, A. J., Norman, L. R., Paul, M. H., and Gibson, W.: External Electric Stimulation of the Heart in Cardiac Arrest. Arch. Int. Med. **96:** 639 (Nov.), 1955.

Of 37 patients with recent Stokes-Adams attacks, 25 required resuscitation with an external electric cardiac pacemaker. It resuscitated them repeatedly from ventricular standstill and maintained an adequate circulation for as long as 5 days during persistent standstill. Ten survived 1 to 24 months after resuscitation. From these experiences a program for the treatment of Stokes-Adams disease has been developed, combining the use of drugs with the electric pacemaker.

External electric stimulation was also effective repeatedly in resuscitating 3 patients with ventricular standstill, syncope, and convulsions due to reflex vagal stimulation. Ventricular standstill due to digitalis or procaine amide was terminated by external cardiac stimulation in 4 patients. In 5 patients the external pacemaker resuscitated the heart from unexpected circulatory arrest due to ventricular standstill. In 7 other patients it was ineffective in the presence of ventricular fibrillation or myocardial unresponsiveness due to anoxia from delay in treatment. Prompt external application of the electric pacemaker should be carried out in these emergencies before one resorts to thoracotomy and cardiac massage.

Bernstein

Congenital Aortic Stenosis

Clinical Aspects and Surgical Treatment

By DANIEL F. DOWNING, M.D.

Thirty-seven patients with congenital aortic stenosis have been studied. Only a few were without symptoms referable to the defect. Characteristically, the patients had a loud, harsh systolic murmur, accompanied by a thrill, to the right of the sternum. On x-ray examination the most frequent manifestation was dilatation of the ascending aorta. Electrocardiographic evidence of left ventricular hypertrophy was found in 60 per cent. Nineteen patients have been operated upon with 2 deaths. The procedure has been tolerated amazingly well. Although it is too early to judge the results, all but 2 of the surviving patients appear to have been helped.

DURING the development of the left ventricular outflow tract and of the aortic valve certain normal processes may be disturbed so that the output of blood is obstructed postnatally. As in similar aberrations of evolution of the right ventricular outflow tract, the obstructing tissue may be proximal to the valve, or the valve cusps may be fused along their margins,* leaving a contracted orifice distally. Wherever the site of interference with flow, the physiologic effect is the same: difficulty in the ejection of blood from the left ventricle and the danger of insufficient oxygen supply to the myocardium, to the brain, and to other less vital tissues.

Relatively little attention has been given the malformation recently. Young[1] reported 10 patients believed to have infundibular stenosis, but no physiologic or anatomic studies were performed. In 1947, Grishman, Steinberg, and Sussman[2] presented data on 23 patients, 3 of whom were autopsied. In addition to physical findings, they described pulse tracings, electrocardiograms, and x-ray photographs. Brofman and Feil[3] were convinced, on the basis of their observations in 10 patients, that the diagnosis of infundibular aortic stenosis can be made by reference to arterial pulse tracings. Forty patients believed to have congenital aortic stenosis were studied by Campbell and Kauntze.[4] Four were autopsied; the diagnosis in the remainder was based primarily on clinical data. Smith and Matthews[5] considered 5 cases of aortic stenosis, 3 of which were proved, and referred particularly to bicuspid aortic valves. The phonocardiogram and the arterial pulse were believed diagnostic in the 15 patients of Reinhold, Rudhe and Bonham-Carter.[6] Twenty-eight patients were reviewed by Marquis and Logan[7]; 3 were autopsied; in 6 surgery was performed; and in the remainder clinical observations were believed to be diagnostic.

Because the anomaly can sometimes be helped by surgery and because our observations differ from those presented in the literature, those cases seen here in the past 3 years are analyzed.

SUBJECTS

Thirty-seven individuals have been studied. A diagnosis of congenital heart disease had been made at birth in 9, within the first year of life in 16, and before the fourth year in the remainder. In none was there a history of rheumatic fever nor any illness suggestive of it. There was a definite sex predilection, there being 29 males and only 8 females; while the age range at the time of diagnosis was 4 months to 39 years.

The diagnosis was confirmed by autopsy in 4 patients, 2 of whom had valvular and 2 infundibular

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* Because of the familiarity with the terms "infundibular" and "valvular" stenosis in reference to the right heart, they will be used in this paper in preference to "subaortic stenosis" and "aortic stenosis."

stenosis. An additional 16 patients had valvular stenosis and 1 had infundibular obstruction at surgery.

Associated cardiac and vascular malformations. The most common accompanying abnormality was coarctation of the aorta. It was demonstrated by thoracic aortography in 4 patients, confirmed by surgery in 2 and by autopsy in 1. The fourth was shown by the contrast study to have generalized hypoplasia of the descending aorta from the region of the left subclavian artery to the diaphragm. Four other patients had evidence of obstruction in the distal aorta with weak or absent femoral pulsations and lowered blood pressure in the legs.

Pulmonary stenosis was present in 3 patients, but it was not of physiologic significance. In addition, 1 patient had a patent ductus arteriosus, and a patent ductus was also present in 1 patient with coarctation of the aorta.

Of the patients with infundibular stenosis found at autopsy, a defect in the membranous portion of the interventricular septum was present in 1, and the right coronary artery was absent in the other.

Methods

A complete history and physical examination, conventional x-ray and fluoroscopic studies, and electrocardiograms with 12 or 14 leads were secured in all patients.

Right heart catheterization was completed in 31 patients, in 1 patient the left side of the heart was simultaneously catheterized, in another, right and left sides were catheterized at different times. Pressures were measured by means of a capacitance-type electromanometer, recorded directly and calibrated with a mercury manometer. Blood samples were analyzed for oxygen content by the method of Van Slyke and Neill.[8] Cardiac output was determined by use of the Fick principle in those in whom oxygen consumption was measured.

Thoracic aortography was performed in 6 patients. In all a Lehman catheter* was introduced into the brachial artery and guided to the ascending aorta, where radiopaque material was injected.

Brachial artery pulse tracings were secured in all but 3 of the group. Pressure was recorded during the resting state and during the Valsalva maneuver when possible. In young children who were anesthetized, the Valsalva effect was obtained by inflation of a blood pressure cuff about the chest or by manual compression of the thorax while mouth and nares were held closed. In a few, the desired response resulted from induced coughing.

Results

History

Pregnancy. In no instance was a history obtained of an exanthematous disease during gestation. The only abnormalities concerning which definite information was available were nausea and vomiting during the first trimester in 5 cases and nausea and vaginal bleeding in 1. The date of conception and the age of the parents were without significance. No patient was born prematurely.

Growth and Development. Weight gain during infancy was slow in 3 of the 29 for whom figures could be obtained, as was motor development.

Symptoms

No Symptoms. Four patients were considered by parents and physicians to be entirely asymptomatic.

Fatigue. Some degree of exercise intolerance was noted in 30 cases. It was marked in 20, with 1 or 2 flights of stairs or blocks on the level as the limit of activity before obvious fatigue appeared. Six had been restricted in effort since the discovery of a cardiac murmur.

Shortness of Breath. Objective or subjective evidence of respiratory difficulty on moderate exertion was present in 21. Paroxysmal nocturnal dyspnea did not occur.

Profuse Perspiration. Inquiry concerning this phenomenon was made of 26 patients. It was present in 13, with intolerance of bed clothing even during cold weather and the necessity of a change of sleeping garment during the night.

Syncope and Other Central Nervous System Symptoms. Episodes of syncope occurred in 6 individuals. On one occasion after vigorous exercise another exhibited profound muscular weakness, dyspnea, and slight cyanosis. Ten patients complained of headache, dizziness, or visual disturbances.

Cyanosis. Blueness of the lips had been noted in 5 patients, but in only 1 had it been appreciated prior to the discovery of a cardiac abnormality.

Forcible Cardiac Action. Two children were noted by the parents to have prominent precordial heaving.

Cardiac Failure. One child in the series experienced 2 episodes of heart failure before his third birthday. He was then maintained on digitalis for 4 years and had no symptoms in spite of normal activity. Three other children were known to have been decompensated. One

* U. S. Catheter Co.

adult entered the hospital in severe failure and responded poorly to medical management.

Chest Pain. One patient complained of a sensation of tightness across the chest following exertion. Five had pain or discomfort in the heart area on occasion. It was not severe and did not radiate in any instance.

Paroxysmal Tachycardia. Three had one or more episodes of rapid heart action. In 2 it was shown to be paroxysmal atrial tachycardia.

Epistaxis. Frequent severe nasal hemorrhage was present in 6 patients, and 1 required carotid artery ligation.

Paresthesias. Disturbances of sensation in the lower extremities were present in 3 patients.

Sudden Death. Two patients in the group died suddenly some time after discharge from the hospital and another expired suddenly while in the hospital awaiting surgery, all without apparent precipitating cause.

Physical Manifestations

The physical findings were relatively uniform. Only 3 patients were below normal in development and size; none was superior. Abnormal pulsations of the carotid arteries were present in 3, and thoracic asymmetry in 3.

Cardiac Enlargement. As determined by percussion or location of the apical impulse, cardiac enlargement to the left was present in 9, and was marked in only 1.

Thrill. In only 2 patients was a systolic thrill absent. In the others it was most intense in the region of the systolic murmur and was transmitted to the right side of the neck as a rule.

Systolic Murmur. A loud, harsh systolic murmur was audible in each case, best heard in the second, third or fourth right interspaces near the sternal border. Transmission was wide and in nearly every instance the murmur could be heard over the neck vessels and the entire right hemithorax. Three patients had, in addition, a systolic blow localized to the apex region and another a harsh apical systolic murmur. In a fifth, a harsh systolic murmur could be heard in the second and third left interspaces and it differed in character from that heard to the right of the sternum; this boy had mild pulmonary stenosis and a patent ductus arteriosus.

Diastolic Murmur. Early, blowing diastolic murmurs were present in the aortic area in 6, the pulmonic area in 2, and at the apex in 2. In the child with a patent ductus there was a faint blow throughout diastole in the second left interspace.

Aortic Second Sound This was normal in 17 patients, somewhat accentuated in 6, and inaudible or faint in 14.

Peripheral Pulses. There was inequality of radial pulsations and normal femoral pulsations in 1 patient. In 3 the radial pulse was small bilaterally and the femoral barely palpable. Still another had a good right radial pulse, a weak left, and no femoral pulsations. In 7 additional patients the femoral pulsations were absent or markedly decreased in force. Of these 12 individuals, 9 showed some evidence of coarctation of the aorta.

Blood Pressure. This was determined both by sphygmomanometer and, in 34 cases, by direct measurement through a cannula in a peripheral artery. In general, the former gave a higher reading, the increase in systolic pressure ranging to 38 mm. Hg, with an average of 17 mm., while that in diastole ranged to 44 mm. (average 12 mm). Three individuals had a higher diastolic pressure on direct measurement than by cuff (10, 30, and 34 mm. Hg). If the direct measurements are accepted, the pulse pressure ranged from 12 to 60 mm. Hg, and in only 4 patients was it less than 25 mm.

The pressure, although normal, was higher in the arms than in the legs in 4 patients and of the same order of magnitude in 3. In 3 children with normal or slightly elevated brachial artery pressure, no reading could be obtained in the legs. Comparison in all these cases was made with cuff pressures.

Erythema of Digits. Distinct, chronic redness of the skin over the distal phalanges of the digits was found in 1 child. There appeared to be slight hypertrophy of the tissue in these areas.

X-ray and Fluoroscopy

The pulmonary vascular markings were prominent in 3 patients and normal in the rest. The main pulmonary artery and its

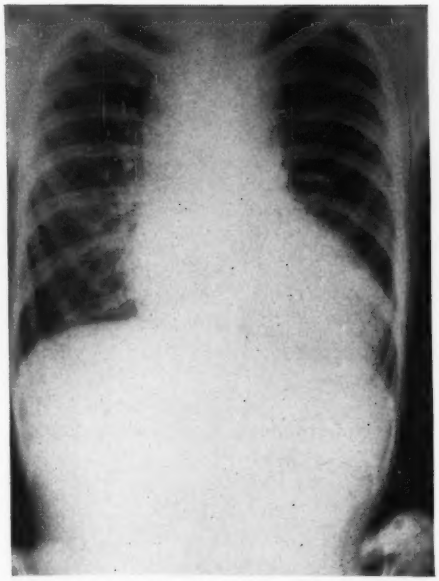

FIG. 1. Enlarged heart with prominent rounding of left border.

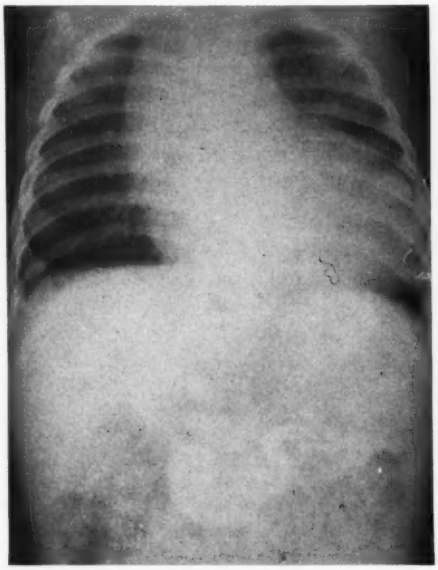

FIG. 2. More marked enlargement and rounding of left border.

branches were either normal or their contour was ill-defined. Pulsations were not remarkable.

The heart contour varied in the postero-anterior projection. In 3 patients there was a

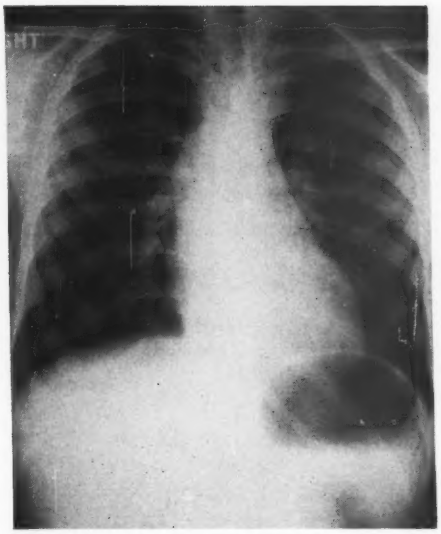

FIG. 3. Ascending aorta prominent and left border lengthened and rounded.

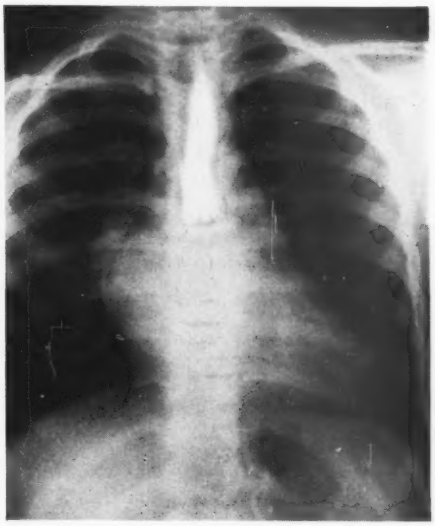

FIG. 4. Prominent ascending aorta, lengthened and rounded left border, and additional bulge of right atrial appendage.

widened supracardiac vascular shadow with straight borders. The heart was enlarged and there was prominent rounding of the left border (fig. 1). Each had a localized coarctation of the aorta and 1, in addition, a hypoplastic descending thoracic aorta. In a fourth

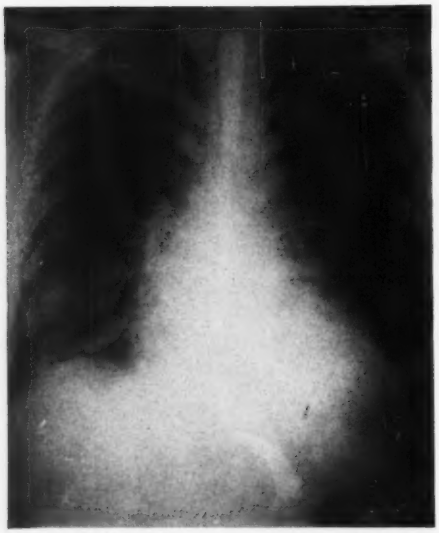

FIG. 5. Enlarged heart, prominent ascending aorta and knob, and depressed apex.

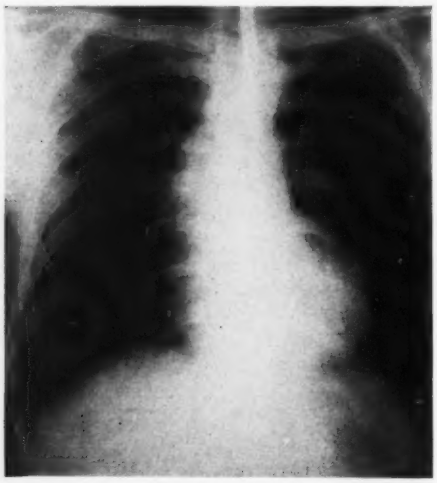

FIG. 6. Enlarged heart, prominent ascending aorta and knob, and squared left border.

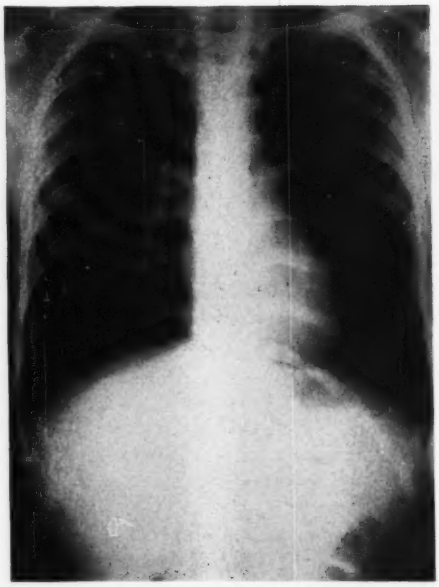

FIG. 7. Normal supracardiac shadow, no cardiac enlargement, and rounded left border.

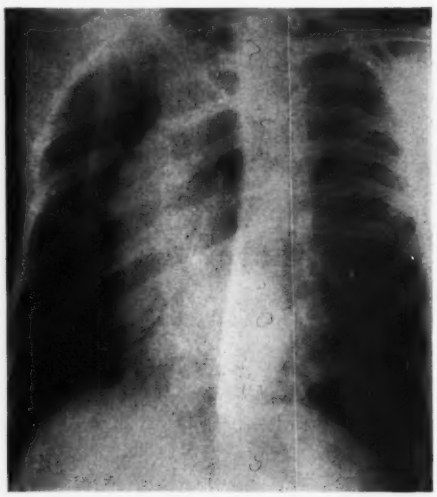

FIG. 8. Dilated and prominent ascending aorta

patient without coarctation, these features were accentuated (fig. 2). The ascending aorta was prominent to the right of the spine and the left border was lengthened and somewhat rounded in 12 patients (fig. 3). The child with pulmonary stenosis and a patent ductus arteriosus had, in addition, a bulge in the region of the right atrial appendage (fig. 4). Four adults had enlarged hearts and prominence of the ascending aorta and of the aortic knob; in 3 the apex was depressed (fig. 5), in the other, the left border was squared (fig. 6). The remaining 17 patients had a normal or slightly narrowed supracardiac shadow, slight or no

cardiac enlargement, and a rounded left border (fig. 7).

In 16 patients there was some enlargement of the right ventricle, the level of encroachment of the anterior heart shadow on the retrosternal space in the right anterior oblique projection being used as the criterion.

Some degree of left atrial enlargement was present in 7 patients; it was graded as 1 plus in 4, 2 plus in 1, 3 plus in 2.

The most consistent roentgen abnormality was dilatation and anterior prominence of the ascending aorta in the left anterior oblique view (fig. 8). It was definite in 29, questionable in 1, and absent in 7.

Only 1 patient had an abnormality of the thoracic bony structures; in this case notching of the inferior border of several ribs was associated with coarctation.

Four patients, 3 with coarctation, were demonstrated to have marked posterior indentation of the esophagus at the level of the transverse arch in the left anterior oblique view. The posteroanterior esophagram showed indentation of the left border in this area.

Calcification of the aortic valve was visible in 2 patients.

Electrocardiogram

The tracings of 7 patients were normal. Five had nonspecific changes of S-T segment or T wave. Two had left bundle-branch block. One showed the pattern of a septal infarct. The remaining 22 showed left ventricular hypertrophy. The rhythm was normal in all except 1 adult with left bundle-branch block who had 2:1 atrial flutter.

Cardiac Catheterization

Cardiac output was found to be within normal limits in all patients in whom oxygen consumption could be measured. In only 1 was it determined both at rest and during exercise; it was found to rise only slightly during the latter phase.

In no case was there evidence of an intracardiac shunt. One child had a significant rise in the oxygen content of pulmonary artery blood.

Four in the series had a definite although slight gradient in systolic pressure between right ventricle and pulmonary artery (6, 10, 12, and 16 mm. Hg), which was constant on repeated withdrawal of the catheter tip from vessel to chamber. One of these was the boy with a left-to-right shunt at the pulmonary artery level; his pulmonary pressure was somewhat elevated (38/10 mm. Hg).

Six additional patients had hypertension in the pulmonary artery, the pressures being 30/20, 45/20, 42/25, 30/10, 110/60, and 80/68 mm. Hg. The pulmonary venous capillary pressure was measured in only 20 patients, among them 3 with pulmonary hypertension. The mean pressure was 10 mm. or more in 9.

Thoracic Aortography

Successful visualization of the whole thoracic aorta was secured in 4 patients. In all, the ascending aorta was dilated and a definite area of coarctation distal to the left subclavian artery could be seen in 3. In the fourth the descending aorta was hypoplastic.

In 1 infant the catheter tip could not be manipulated into the aorta. Injection of contrast material was made into the right subclavian artery. The innominate artery was seen to be greatly dilated but opacification of the arch was unsatisfactory. The ascending aorta of another individual could not be entered and the opaque substance was injected into the distal portion of the arch; this section of the vessel was found to be dilated and below it was an area of coarctation; the descending aorta was also dilated for a short distance.

In the section on X-rays it was mentioned that 3 patients had posterior indentation of the barium-filled esophagus. The aortogram in each indicated that this was due to compression by the dilated arch.

Brachial Artery Tracings

Of the 34 tracings obtained, not one could be considered normal. A slow rise to the peak of systole was almost universal. Five types of curve were seen: (1) a definite anacrotic notch or slur; (2) a double systolic peak; (3) a notch or slur on the dicrotic limb near the summit, with a distinct dicrotic incisura below; (4) a smooth curve, with a particularly small pulse

pressure; (5) a curve with many vibrations on both limbs and a very small pulse pressure.

The curves were analyzed in relation to various other data: Character of aortic second sound, electrocardiogram, roentgen findings, site of obstruction, degree of stenosis found at operation. The only significant correlation was association of types 4 and 5 with stenosis of the greatest severity.

Discussion

The diagnosis of aortic stenosis in only 3 infants (age under 2 years) is somewhat surprising in view of the relatively large number in this age group who underwent cardiac study. One explanation involves the common failure of the physician to place the stethoscope head over the right second and third interspaces. Another is that the physical findings may not suggest the diagnosis until after a period of time. Five of these patients did not have evidence of aortic stenosis when they were first studied. None had the typical murmur and thrill. Each was catheterized and nothing of significance found. At subsequent re-examinations the physical findings changed. Initially, there was a systolic murmur to the left of the sternum in 4 patients and over the xiphoid in 1. As each individual grew older the murmur changed, becoming most prominent in the aortic area, and then louder and harsher. In 3 of these patients, electrocardiographic evidence of left ventricular hypertrophy was present before the typical signs of aortic stenosis developed. The explanation of these changes is not entirely clear. They are probably due to change in position of the aortic valve and to relative increase in severity of the stenosis with increase in body and heart size.

The site of obstruction is known in 21 cases. It was valvular in 18. If these are a fair sample of the entire series, only 1 or 2 additional patients had infundibular stenosis.

The anomalies associated with aortic stenosis in this group are of interest. Pulmonary stenosis of physiologically insignificant degree occurred in 4 patients. One of these also had a patent ductus arteriosus. A ventricular septal defect was present in 1 boy who had infundibular stenosis. In another patient with infundibular stenosis only the left coronary artery was found, with a healed infarct of the interventricular septum. Coarctation of the aorta was the most common accompanying lesion; it was present in 8. A patent ductus was also found in 1 of these 8 patients. All patients with coarctation should therefore be carefully examined for evidence of aortic stenosis.

The greater the degree of obstruction the greater the cardiac burden, and the greater the cardiac reserve the greater the ease with which the burden is carried. *Fatigue* on moderate exertion indicates an insufficient transport of oxygen to the muscles, because the left ventricle is not able to meet the demands made upon it. *Shortness of breath* also indicates an insufficient reserve. Increase in rate of cardiac contraction does not meet the need for oxygen, so more air per unit of time is brought to the alveoli by increased respiratory rate. Actual *dyspnea* can be accounted for by great respiratory demand or by pulmonary edema consequent upon left ventricular failure. *Syncope* and other central nervous system symptoms may be explained on the basis of a temporary inadequacy of oxygen supply to cerebral tissue, due to a transient failure of the left ventricle to maintain output. The cerebral symptoms may result from other causes, such as aortic or carotid reflexes initiated by dilatation of the ascending aorta or conditions of aortic flow. *Chest pain* is due to myocardial ischemia because of inadequate coronary flow. Cardiac output may be normal and coronary flow normal, but because of hypertrophy of the left ventricular fibers the demand is greater than normal. In this series, pain was not so frequent or severe as in a similar group with acquired aortic stenosis. *Sudden death* indicates that left ventricular output can be acutely diminished to a degree that myocardial function is no longer possible. That the circumstance need not be one of severe stress is shown by the sudden collapse and death of one patient while walking across a schoolyard. Another was walking along the beach when he suddenly died. The third was in the hospital awaiting surgery, when she died without warning. A fourth child with undoubted aortic stenosis, but seen only in consultation and not included

in the series, also died suddenly during a period of quiet activity that had not been preceded by violent exertion. Carotid sinus reflexes rather than acute left ventricular failure may at times be the cause of sudden death.

The harsh *systolic murmur* in the second and third right interspaces must be due to the passage of blood beyond a narrowed outlet. A murmur in this location is found rarely in other congenital heart malformations. The early *diastolic murmur* in the aortic, pulmonic, or apical regions probably reflects a degree of aortic insufficiency. In one patient with an apical diastolic murmur, resection of the coarcted segment of the aorta was followed by disappearance of the murmur.

The abnormal roentgen features consist, in the main, of prominence of the ascending aorta, rounding or lengthening of the left cardiac border, and right ventricular or left atrial enlargement. Gross cardiac enlargement is not frequent. The dilatation of the ascending aorta may well be due to the same mechanism offered to explain poststenotic dilatation of the pulmonary artery.[9] A jet of blood entering the vessel through a narrow orifice that is eccentrically placed strikes the wall and causes a localized systolic bulge. As time goes on, the constant trauma brings about generalized stretching. Rounding of the left cardiac border is due to hypertrophy of the left ventricular myocardium. Greater degrees of hypertrophy will depress the apex and cause lengthening of the border. Gross enlargement of the chamber appears when there is dilatation as well as hypertrophy. Left atrial enlargement is due to a back-pressure phenomenon. The patients with undoubted right ventricular prominence had pulmonary hypertension.

Pulmonary hypertension in the patient with an accompanying patent ductus might be explained on the basis of narrowed pulmonary vessels and increased resistance as a result of blood flow through the ductus. His pulmonary venous capillary pressure was normal. To account for pulmonary hypertension in the others presents some difficulty. Obviously, left ventricular failure would lead to incomplete emptying of the chamber with consequent overfilling and increased pressure in the left atrium and pulmonary veins. A higher pressure head would then be necessary on the other side of the capillary bed. However, none of the patients with pulmonary hypertension showed evidence of left ventricular failure. Rather than dynamic failure of the left ventricle, a failure in capacity may be considered. Because of obstruction to outflow the chamber wall undergoes concentric hypertrophy, which, in the absence of dilatation, eventually diminishes the capacity due to encroachment of the wall. At some point the capacity decreases minutely, so that ventricular systole occurs before the left atrium has completely emptied. With repetition of the process the residual in the left atrium and pulmonary veins becomes substantial. With resistance to outflow the pressure rises in the left atrium and pulmonary veins and is accompanied by a rise in pressure on the other side of the pulmonary capillary bed. Vascular changes diminish the caliber of small pulmonary vessels; increased resistance results and leads to further hypertension. Thus, in a way, the responsibility for maintaining the circulation is gradually shifted, more and more, to the right ventricle.

We have studied a large number of *brachial artery tracings* of patients with various types of congenital and acquired heart disease and of many with no heart disease or insignificant lesions. In those with aortic stenosis, whether congenital or acquired, certain abnormalities have been noted in the majority that are not pathognomonic. Some are seen in other congenital and acquired conditions, although not so frequently. Their genesis is not clear. Experimental studies are under way which, it is hoped, will shed some light upon the problem.

Diagnosis

To the present time we have studied several hundred patients, proved at operation or autopsy to have aortic stenosis, either congenital or acquired. As a result of this experience we believe that an individual with a loud, harsh systolic murmur in the region of the second and third right interspaces near the sternum that is transmitted to the neck vessels and is accompanied by a thrill may be considered to have aortic stenosis. The diagnosis is

more certain if the electrocardiogram shows left ventricular hypertrophy, if there is dilatation of the ascending aorta on roentgen examination, and if there is an abnormal brachial artery tracing. Certain proof is established by successful left heart catheterization. This procedure entails the percutaneous puncture of the left atrium by a needle with passage of a small gage catheter through the ventricle and into the aorta. A gradient in systolic pressure from aorta to ventricle is pathognomonic of obstruction at or near the aortic valve. If the aorta is not reached, comparison of pressures in the left ventricle and the brachial artery is significant. Flow across the valve is a determinant in judging severity of stenosis, and simultaneous right heart catheterization with estimation of cardiac output is of great importance in some cases.

The author has had no personal experience with the procedure, but it has been accomplished in our laboratory in 350 individuals. On the basis of stand-by observation it appears unwarranted in those patients that are thought to have aortic stenosis. The diagnosis and the estimation of its severity can be made on data derived from routine studies and right heart catheterization.

The preoperative localization of the exact site of obstruction seems, at present, to be impossible. Absence of the aortic second sound has not been a constant feature in our cases with proved valvular stenosis. The character of the arterial pulse tracing has varied so widely that it appears to be of no diagnostic value. It was hoped that left heart catheterization would be of aid. In 1 patient in this series, however, proved to have infundibular stenosis, combined catheterization of right and left sides was performed. When the catheter tip was withdrawn from aorta to ventricle an abrupt transition was seen from a tracing typical of a great vessel to that of a high pressure ventricle. There was no intermediate zone of low systolic pressure and a ventricular curve as is sometimes seen in pulmonary stenosis.

Treatment

Aortic stenosis is the only congenital cardiac anomaly compatible with a relatively long span of years that requires restriction of activity. The dynamics of other defects, such as pulmonary stenosis, septal defects, coarctation of the aorta, permit the patient's subjective response to exertion—muscle fatigue and shortness of breath—to insure a margin of cardiac reserve. Aortic stenosis constantly threatens acute coronary insufficiency. The margin between adequate and inadequate coronary flow is small; activity demanding greater cardiac output may quickly exhaust reserve and lead to sudden myocardial failure.

The development of a satisfactory surgical procedure for the relief of aortic stenosis has been described by Bailey.[10] It had proved feasible in the correction of the congenital malformation in 7 adult patients. Its application in the child was delayed because the transventricular approach was thought to require a large chamber and because the transaortic approach would require a relatively huge ascending aorta.

The sudden death of 3 children within a short period of time made it obvious, however, that the risk of doing nothing might well be greater than the risk of operation. Surgery was therefore performed in the next patient, a 6-year-old boy in whom the diagnosis of significant aortic stenosis was made. The transventricular approach was used, a dilator being introduced into the left ventricle through an incision near the apex. It was passed into the valve area with considerable difficulty and opened. Immediately, the previously strong thrill over the ascending aorta became feeble. The procedure was tolerated extremely well, with cardiovascular changes no more severe than would be met during a simple thoracotomy.

Since that time operation has been recommended for all children found to have a physiologically significant lesion. A total of 19 patients have been operated upon, 10 of them children. Two were only 3 years of age.

There has been 1 operative death, a 36-year-old man in irreversible failure, who accepted surgery as a desperate measure. Cardiac arrest occurred before any definitive procedure could be carried out.

Another patient, age 18, was improved post-

operatively, in that his exercise tolerance was greater. Eight months following surgery, while dancing, right hemiplegia occurred, and 2 days later he died. At autopsy an area of necrosis was found in the left cerebral hemisphere, with a small particle of calcium in the center. There was no old or recent infection. The aortic valve orifice was adequate in size, but not calcified. Whether nor not the calcified particle was an embolus from the valve could not be determined.

One patient, age 19, proved to have infundibular stenosis at operation, was studied by means of combined right and left heart catheterization before and after operation. The systolic gradient from left ventricle to aorta preoperatively was 140 mm. Hg. The cardiac output was 4 L./min. Postoperatively the gradient was 80 mm. Hg and the cardiac output was 2.4 L./min. Although the gradient was smaller, the cardiac output, too, was significantly less. She has shown no clinical improvement. Operation in this patient must be considered a failure.

In the remaining 16 patients, there has been objective evidence of improved flow across the aortic valve. In them the prominent systolic thrill and murmur over the ascending aorta became softer following commissurotomy, a common localized systolic jet-impulse disappeared. In 3 the thrill disappeared.

Symptoms were relieved in 14 of 15 patients. One was asymptomatic although he had been in cardiac failure in early life. Exercise tolerance and respiratory reserve improved, central nervous system manifestations and chest pain stopped, and, as a rule, weight gain has been accelerated in growing children.

The one patient, an 18-year-old girl, who has not improved symptomatically, was operated upon 2 months ago. She has developed signs of aortic insufficiency, and, after temporary improvement, her fatigue and dyspnea are now greater than preoperatively. Her postoperative care, however, has not been well supervised, in that ambulation was allowed too early and her activities following discharge were not controlled.

Aortic insufficiency as a result of operation is of great import. In 2 additional patients an early blowing diastolic murmur appeared, but without other signs of aortic regurgitation, and symptoms definitely improved. They are not considered to have dynamically significant aortic regurgitation. Surgery was performed on 8 of the 11 patients with early diastolic murmurs on initial examination. One was the girl with infundibular stenosis who showed no improvement in physiologic data; neither systolic nor diastolic murmur changed. In 3 others, the systolic murmur greatly decreased in intensity, but there was no change in the diastolic murmur. In 4, the diastolic murmur could not be heard postoperatively; in them the improved mobility of the stenosed aortic valve seemed to have removed the element of incompetence.

Complications during and after operation have been surprisingly few. Of the living patients, 2 had a stormy postoperative course. One, the girl who now shows aortic insufficiency, was, through error, allowed out of bed in spite of evidence of cardiac failure. A number of thoracenteses were also done, probably unnecessarily. The other, a boy of 14, developed a severe wound infection that was slow to heal. In all, the procedure itself was extremely well tolerated, cardiac arrest or ventricular fibrillation being no source of concern. Ambulation was allowed on the tenth postoperative day in children, and they were allowed to go home on the same day.

It is certainly too early to make any sweeping statements about the operated group, beyond the fact that 14 of the 17 surviving patients have been symptomatically improved. We believe that, in all, the danger of sudden death has been removed. In the children it is possible that residual stenosis may become relatively more severe with increased growth. If so, a second operation may be successful.

The indication for surgical relief of congenital aortic stenosis is the presence of the physiologically significant lesion. It is significant if one or more of the following criteria is demonstrated: (1) troublesome symptoms such as fatigue, shortness of breath, syncope; (2) electrocardiographic evidence of left ventricular hypertrophy; (3) some degree of pulmonary artery hypertension or pulmonary

venous hypertension in the absence of other lesions; (4) a systolic gradient of 50 mm. Hg or more across the aortic valve, with a normal or decreased cardiac output.

The time of election for operation is the time that indications appear, whether it be at 3 months or 30 years. No one can tell when compensation may fail. There is no optimal age; there is only the age of opportunity.

Summary

The clinical and physiologic data of 37 patients with aortic stenosis have been presented.

Fatigue, shortness of breath, and profuse perspiration were the commonest symptoms. Central nervous system manifestations and chest pain were infrequent. A systolic thrill and murmur in the second and third right interspaces were almost universal. Because they are found in this location very rarely in other malformations, they are of great diagnostic significance. Right heart catheterization is very helpful in ruling out other lesions. Left heart catheterization is diagnostic if a gradient in systolic pressure across the valve is demonstrated.

Differentiation of valvular from infundibular stenosis has not been possible in this series.

Because of the danger of sudden death, relief of severe obstruction is mandatory.

A satisfactory operative procedure is available for correction of valvular stenosis. It involves the dilatation of the narrowed orifice by means of an instrument inserted into the left ventricle.

Nineteen patients have been operated upon. There was one operative death and another died 8 months later. One patient, with infundibular stenosis, is unimproved; 1 is symptomatically worse; 1 had no symptoms prior to surgery. The remaining 14 have experienced gratifying relief of symptoms.

Summario in Interlingua

Es presentate datos clinic e physiologic ab 37 patientes con stenosis aortic.

Fatiga, dyspnea, e profuse transpiration esseva le symptomas le plus commun. Manifestationes del systema nervose central e dolores thoracic esseva infrequente. Un systolic fremito e murmure in le secunde e tertie interspatios dextere esseva quasi general. Proque illos es rarissime in iste sito in altere malformationes, illos possede un alte grado de signification diagnostic.

Catheterisation dextero-cardiac es de grande adjuta in le exclusion de altere lesiones. Catheterisation sinistro-cardiac es diagnostic per le demonstration de un gradiente de pression systolic a transverso le valvula.

Le differentiation inter stenosis valvular e stenosis infundibular non esseva possibile in le presente serie.

A causa del risco de morte subitanee, le alleviation de sever obstructiones es obligatori.

Un satisfacente technica chirurgic es disponibile pro le correction de stenosis valvular. Illo effectua le dilatation del restringite orificio per medio de un instrumento inserite in le ventriculo sinistre.

Dece-nove patientes esseva operate. Il habeva un morte operatori; un secunde patiente moriva 8 menses plus tarde. Un del patientes—un caso de stenosis infundibular—monstra nulle melioration; in un altere le symptomas es pejor; un caso esseva sin symptomas ante le intervention chirurgic. Le remanente 14 patientes ha experientiate grados gratificante de melioration in lor symptomas.

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The study was undertaken to determine whether or not training in the athlete altered the methods of oxygen transport employed during mild to moderately severe exercise.

Cardiac catheterization was carried out on 3 track men, 2 of whom were studied before training and again during training. Cardiac output, A-V oxygen differences, and pulmonary arterial pressures were obtained during rest and mild and moderately severe exercise. In addition, the effect of training on maximum breathing capacity and vital capacity was determined.

The cardiac output and arteriovenous O_2 difference during exercise was no different in the trained than in the untrained individual. Vital capacity was not changed by athletic training; however, the maximum breathing capacity was increased by training. Pulmonary arterial pressure increased in response to all grades of exercise regardless of training.

Training produced no difference in the way the individuals met the tissue demands for an increased supply of oxygen during exercise up to levels requiring 2 liters of oxygen intake a minute. Up to this level of oxygen consumption, the contributions of increased cardiac output and increased oxygen extraction from arterial blood to an increasing rate of oxygen consumption are roughly equal.

The results of this study indicate that athletic training does not change the method by which the athlete meets the tissue demands for an increased supply of oxygen during exercise up to levels requiring 2 liters of oxygen a minute.

WECHSLER

Relative Contribution of Blood from Each Lung to the Left-to-Right Shunt in Atrial Septal Defect

Demonstration by Indicator-Dilution Technics

By H. J. C. Swan, M.B., Peter S. Hetzel, M.D., Howard B. Burchell, M.D., and Earl H. Wood, M.D.

Arterial dilution curves of T-1824 have been recorded by oximeters after injection of T-1824 into both the right and left pulmonary arteries in patients with anomalous connections of the pulmonary veins, with atrial septal defects or with persistent common atrioventricular canals. The most extreme differences were found between the pairs of curves in the patients with the anomalous connection. These differences were less pronounced but clearly recognizable in the other conditions, and suggested a more general use of the term "anomalous pulmonary venous drainage." The findings indicate that, in the usual case of atrial septal defect, a greater proportion of the blood from the right lung passes to the right atrium than does blood from the left lung.

THE term "anomalous pulmonary venous connection" has been proposed to designate the anomaly of a pulmonary vein passing to the right atrium or to a tributary thereof.[1, 2] Such a term also may include the condition in which a pulmonary vein communicates with the left atrium by way of an abnormal venous channel.[3] It is thought that the term "anomalous pulmonary venous drainage" applies more appropriately to any hemodynamic situation in which blood from the pulmonary veins passes into the right atrium and is recirculated through the lungs.

Within the limits of these definitions, anomalous pulmonary venous drainage is a relatively common condition, since it includes the usual case of atrial septal defect in addition to cases of anomalous pulmonary venous connection. However, atrial septal defects frequently are found in patients who have anomalous pulmonary venous connections. Furthermore, some examples of anomalous connection are associated with a larger atrial septal defect, the posterior margin of which cannot be defined. In these cases, anomalous pulmonary veins usually pass into the lateral wall of the right atrium about midway between the superior and inferior venae cavae and lie in the plane of the inferior vena cava. Since it is probable that such an anomalous connection is a consequence of the size and location of the atrial septal defect, it has been termed "secondary anomalous pulmonary venous connection."[4] Anomalous connections into the inferior vena cava, into the junction of the superior vena cava with the right atrium or at other positions predictable on the basis of developmental anatomy, are found[1] and these may exist with or, less frequently, without an associated atrial septal defect. In certain examples of anomalous connection of the right pulmonary veins to the junction of the superior vena cava with the right atrium, a considerable proportion of the blood leaving the anomalously connected vein has been demonstrated to drain normally by way of an interatrial communication.

The introduction of these 2 terms, namely, "connection," with its anatomic connotation, and "drainage," with its physiologic or hemodynamic implications, has been necessitated by study of patients with arteriovenous shunts by means of indicator-dilution technics. It is possible by use of these technics to determine the presence and approximate magnitude of anomalous venous drainage in several congenital malformations of the heart. This paper is

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intended to deal principally with the findings in patients with atrial septal defects but, in order to develop the interpretation of the dilution curves in these patients, curves obtained in 3 patients with anomalous pulmonary venous connections also are presented. In addition, the curves in 3 patients with common atrioventricular canals are considered.

The findings indicate that in the *usual* case of atrial septal defect, the greater proportion of the blood shunted from left to right across the defect is returning to the heart from the right lung. This hemodynamic situation represents a position intermediate between that of patients with anomalous pulmonary venous connections, in whom all the blood from one lung passes to the right atrium, and that of patients with ventricular septal defects or patent ductus arteriosus, in whom approximately equal contributions to the left-to-right shunt are made from each lung.

The technic of injection of Evans blue (T-1824) via cardiac catheter directly into the chambers of the heart and great vessels[5] now makes it possible to localize the site of a right-to-left shunt with precision. The extension of this method of study to congenital cardiac disease associated with a left-to-right shunt suggested itself.

Broadbent and Wood[6] have described the essential contour of arterial indicator-dilution curves after injection of T-1824 into a peripheral vein in certain forms of congenital cardiac disease characterized by a left-to-right shunt. The appearance and build-up times usually are normal, but the peak deflection is reduced. The return of dye toward its equilibrium value is slowed, and no peak of concentration due to indicator that has passed through the systemic capillaries and recirculated can be defined on the slope of declining concentration. These authors observed no special feature in such curves that would permit localization of the site of the shunt. When injections are made directly into the great vessels or the chambers of the heart, the resultant curves are more clearly defined and features not evident on curves following peripheral injection can be recognized. In many cases, characterized by blood flowing from a pulmonary vein to the right atrium, differences can be found between curves recorded after injection of dye into the right pulmonary artery and those noted after injection into the left pulmonary artery. These differences are not a feature of ventricular septal defect or patent ductus arteriosus, in which the curves recorded after injection of dye into each pulmonary artery are essentially similar.

Methods

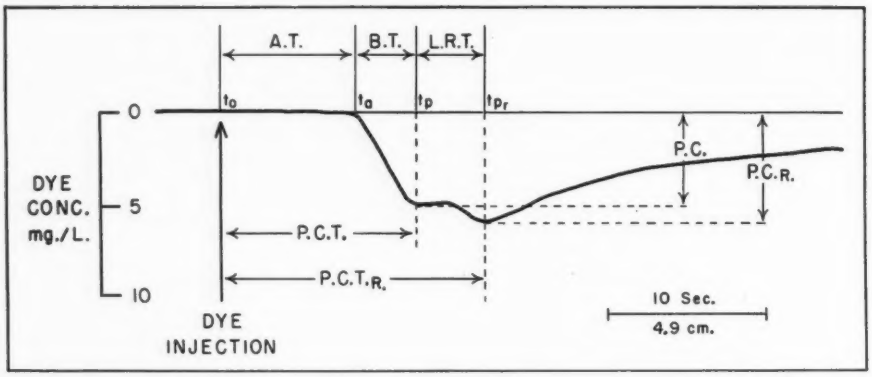
The data presented were obtained from studies on 18 patients, 12 of whom had atrial septal defects. In 2, the defects extended posteriorly to include the orifices of the right pulmonary veins, causing "secondary" anomalous connection of these veins to the right atrium; 3 had anomalous connection of the veins from the right or left lung; and 3 had persistent common atrioventricular canals. The diagnoses were confirmed in all 14 of the patients in whom surgical correction of the defect was undertaken.*

All the patients were studied by the cardiac-catheterization procedure described previously.[7, 8] The locations of intracardiac shunts were determined by the withdrawal of samples of blood through a cuvette oximeter from different positions within the heart and great vessels in rapid succession. The pulmonary and systemic blood flows were obtained by the Fick method when the patient was breathing 100 per cent oxygen. The proportion of blood shunted from left to right was calculated as follows:

$$\frac{\text{Pulmonary flow} - \text{Systemic flow}}{\text{Pulmonary flow}} \times 100 = \text{left-to-right shunt.}$$

Arterial indicator-dilution curves were recorded by earpiece oximeter[9] in each of the patients after injection of T-1824 into both the right and left pulmonary artery and into other sites in the heart and great vessels. With the exception of one patient, dilution curves also were recorded simultaneously by means of a cuvette oximeter[10] through which blood from the radial artery was allowed to flow. Quantitative measurements were made from the latter curves and are reported in a separate publication.[11] The dilution curves from each of these sampling sites were usually similar, but the data presented in this paper have been obtained entirely by means of the ear oximeter. The time and concentration components of dilution curves characterized by a peak of concentration due to pulmonary recirculation are shown in figure 1; the symbols and

* The authors are indebted to Dr. J. W. Kirklin for use of his operative notes.



A.T. - Appearance Time
B.T. - Build-up Time
L.R.T. - Lung (Pulmonary) Recirculation Time
P.C. - Peak Concentration
$P.C._R$ - Peak Concentration (Including 1st Pulmonary Recirculation)
P.C.T. - Peak Concentration Time
$P.C.T._R$ - Peak Concentration (Recirculation) Time

FIG. 1. Time and concentration components of indicator-dilution curves characterized by a second peak of concentration due to dye that has recirculated through the lungs. In these dilution curves, an increase in concentration of dye causes a downward deflection of the recording beam. The symbols t_o, t_a, t_p and t_{p_r} refer to instants of injection, appearance, initial peak, and peak due to recirculated dye, respectively. Note the similarity in contour that this curve bears to those characteristic of a right-to-left shunt, which differ only in having a shorter appearance time.

definitions used conform to those that have been proposed for normal curves.[12]

RESULTS

Hemodynamic findings. The essential data with regard to pressure, flow, and shunt are given in tables 1 and 2. A high proportion of the pulmonary blood flow was found to recirculate through the lungs in the majority of the patients who had atrial septal defects.

Contour of Dilution Curves on Central Injection. When the dye was injected into the pulmonary trunk, the right ventricle, or the inferior or superior vena cava in these patients, it was usually possible to distinguish at least 2 separate peaks of concentration, but these were less well defined as the site of injection was moved more peripherally in each patient. The differences between curves recorded after injection of dye into the pulmonary trunk and, shortly thereafter, into the superior vena cava are noted in figure 2. Comparable changes consisting of prolongation of the time components and reduction of concentration components have been described in persons not having an intracardiac shunt when injections of dye were made at progressively more peripheral sites.[13]

Injection of Dye into Both Right and Left Pulmonary Artery in Atrial Septal Defect. On gross inspection, the most notable characteristic of curves after injection of dye into both the right and left pulmonary artery was the great difference between them. The curves recorded after injection of dye into the left pulmonary artery were more nearly normal. The values for appearance time, *A.T.*, build-up time, *B.T.*, and peak-concentration time, *P.C.T.*, were somewhat less than values in normal persons studied in our laboratory. The build-up slope of the curve was smooth and the peak concentration C_p of dye approached normality. The slope of declining concentration, however, was distorted by an abnormal second peak of concentration that was not clearly defined in certain cases. The interval between the initial (normal) peak and the second peak averaged 4.7 sec. (range = 4.2 to 5.9), which was much less than the normal systemic recirculation time of 20 sec. This short interval is consistent with the concept that the second peak of concentration is due to dye that has traversed a shortened vascular pathway consist

TABLE 1.—*Intracardiac Pressure, Blood-Flow Data, and Circulation Time in Atrial Septal Defect: 12 Cases*

Case*	Age, yr.	Surface area, m².	Pressure, mm. Hg			Blood flow, L./min./M².		Lt.-rt. shunt, per cent	Circulation time, seconds†			
			Pulmonary artery, wedge	Pulmonary artery	Right atrium	Pulmonary	Systemic		Right lung		Left lung	
									A.T.†	P.C.T.	A.T.	P.C.T.
1	27	1.57	12/5	30/15	4/2	10.3	4.4	60	6.0	9.2	4.8	9.3
2	48	1.59	—	127/43	23/16	8.1	2.5	75	9.4	13.0	7.0	12.5
3	40	1.55	8/5	28/7	6/3	11.5	3.3	70	5.9	8.9	4.8	10.7
4	49	1.50	—	40/14	7/2	17.0	2.7	80	4.4	8.0	4.8	9.0
5	24	1.70	11/8	17/8	7/4	17.7	4.2	75	4.9	9.6	5.1	10.0
6	26	1.48	19/12	31/17	6/1	14.8	3.3	75	6.0	9.0	5.0	8.7
7	16	1.75	10/4	25/10	11/5	5.4	2.4	55	6.1	10.4	4.7	9.4
8	29	1.61	18/14	30/10	15/0	13.8	4.8	65	5.6	9.5	6.2	10.5
9	34	1.45	10/6	20/8	4/2	10 2	2.8	70	5.0	8.6	4.0	7.4
10	47	1.59	10	38/19	7/2	8.3	2.8	65	5.0	9.0	4.8	8.6
Associated "secondary" anomalous connection of right pulmonary veins												
11	43	1.67	—	37/19	9/3	11.7	2.4	80	8.8	13.6	5.2	9.0
12	22	1.79	11/4	30/14	8/−1	14.2	3.1	80	6.8	9.5	5.0	8.6

* The diagnosis was verified at operation in all but cases 7 and 10. The dilution curves in cases 1 through 9 are depicted in figure 3; those in case 10 are seen in figure 2*B* and those in cases 11 and 12 are seen in figure 4*B*.

† Circulation time measured by earpiece oximeter. A.T., appearance time; P.C.T., peak concentration time.

TABLE 2.—*Intracardiac Pressure, Blood-Flow Data, and Circulation Time in Anomalous Pulmonary Venous Connection and Persistent Common Atrioventricular Canal: 3 Cases Each*

Case*	Age, yr.	Surface area, m².	Pressure, mm. Hg			Blood flow, L./min./M².		Lt.-rt. shunt, per cent	Circulation time, seconds†			
			Pulmonary artery, wedge	Pulmonary artery	Right atrium	Pulmonary	Systemic		Right lung		Left lung	
									A.T.	P.C.T.	A.T.	P.C.T.
Anomalous pulmonary venous connection (fig. 5*B*)												
13‡	44	1.78	11/5	22/7	6/1	8.2	5.3	40§	10.0	15.0	5.0	9.0
14‖	33	1.80	17/9	29/13	11/5	7.2	3.4	50§	5.6	11.1	6.5	18.6
15‡	32	1.58	—	27/10	2	8.4	4.5	45§	9.0	14.0	5.4	9.2
Persistent common atrioventricular canal (fig. 6*B*)												
16	25	1.36	12/6	31/10	7/2	14.7	3.9	70#	5.6	10.2	5.1	9.4
17	27	1.50	10/7	23/8	8/5	8.9	2.8	70#	5.8	9.5	5.2	9.1
18	28	1.60	8/5	27/10	7/2	11.6	3.5	70#	5.0	9.1	4.9	8.4

* The diagnosis was verified at operation in all but cases 13 and 18.

† Circulation time measured by earpiece oximeter. A.T., appearance time; P.C.T., peak concentration time.

‡ Anomalous venous connection from right lung to inferior vena cava.

§ Left-to-right shunt at the atrial level.

‖ Anomalous venous connection from left lung to innominate vein.

Total left-to-right shunt at the atrial and at the ventricular level.

ing of the pulmonary vessels, right atrium, and right ventricle.

The most obvious feature in the curves obtained after injection into the right pulmonary artery was the reduction in the initial peak of concentration. The magnitude of this peak varied widely between individual patients. The average appearance time for curves following

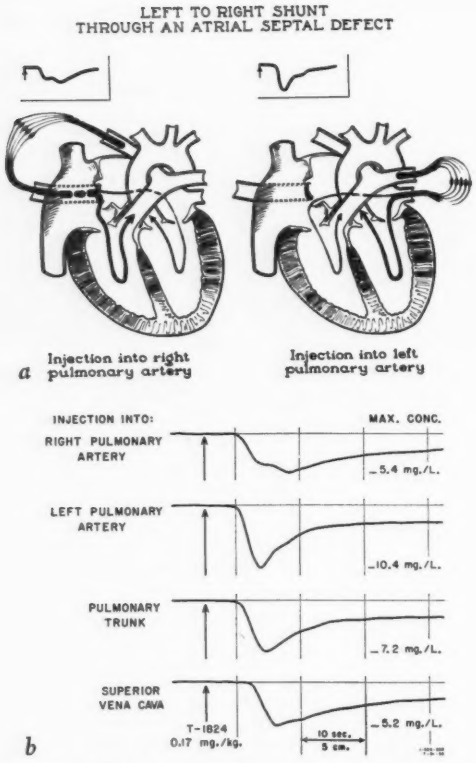


FIG. 2. The path taken by indicator dye after its injection into both the right and left pulmonary artery and the resultant dilution curves recorded in the systemic arterial system in a case of atrial septal defect (case 10).

A. Diagrammatic representation of the central circulation. The thick solid lines within the diagram represent the circulatory route taken by the indicator after its injection. The relative thickness of these lines represents the fraction of indicator passing to different locations from the left atrium. The small inserts above each diagram represent the general contour of a dilution curve from each site of injection, with the instant of injection indicated by the arrow. Note the proximity of the right pulmonary veins to the location of the septal defect, which is evident from pathologic anatomic studies of this condition.

B. Systemic arterial dilution curves recorded by ear oximeter (table 1). Injections of T-1824 were made at the sites indicated to the left of the figure. The curves have been arranged vertically in relation to the instant of injection indicated by the arrow. The values for the maximal concentration of dye attained in radial arterial blood recorded simultaneously are tabulated to the right and serve to indicate the sensitivity of the instrument.

injection into the left pulmonary artery was 5.1 sec. and that following injection into the right pulmonary artery was 5.8 sec. The second peak of concentration, which was poorly defined on the declining slope of the curve after injection into the left pulmonary artery, appeared as a much larger deflection when dye was injected into the right pulmonary artery (fig. 3). The secondary deflection in this series of patients was usually somewhat greater than the initial peak of concentration.

In 2 cases (11 and 12 in table 1) in which the interior of the right atrium was explored at operation, the right pulmonary veins appeared to enter directly into the chamber of the right atrium, giving rise to a "secondary" anomalous connection. The most abnormal pairs of curves of the group studied were obtained in these 2 cases (fig. 4). The dilution curve obtained in each of these cases after injection of indicator into the left pulmonary artery was abnormal, with a reduced peak concentration and a prolonged disappearance slope. The curves following injection into the right pulmonary artery were even more abnormal. In case 12 (fig. 4*B*) there was a very small initial deflection followed by a large secondary deflection, while in case 11 (same figure) the appearance of dye was delayed 3.6 sec. when compared to the dilution curve recorded following injection into the left pulmonary artery. This is a greater difference than that seen between any pair of curves in the other patients with atrial septal defect, and its significance is considered below.

Anomalous Pulmonary Venous Connection. This anomaly was present in 3 cases (fig. 5). In cases 13 and 15 (fig. 5*B*), the veins from the right lung connected to the inferior vena cava below the diaphragm, whereas in case 14 the veins from the left lung connected with the left innominate vein. The interatrial septum was thought to be intact in case 13, while an atrial septal defect coexisted in cases 14 and 15. In each of these cases, one of the dilution curves showed a nearly normal peak concentration, but the slopes of declining concentration were abnormal in cases 14 and 15. In contrast, the dilution curves recorded after injection into the other pulmonary artery were grossly ab-

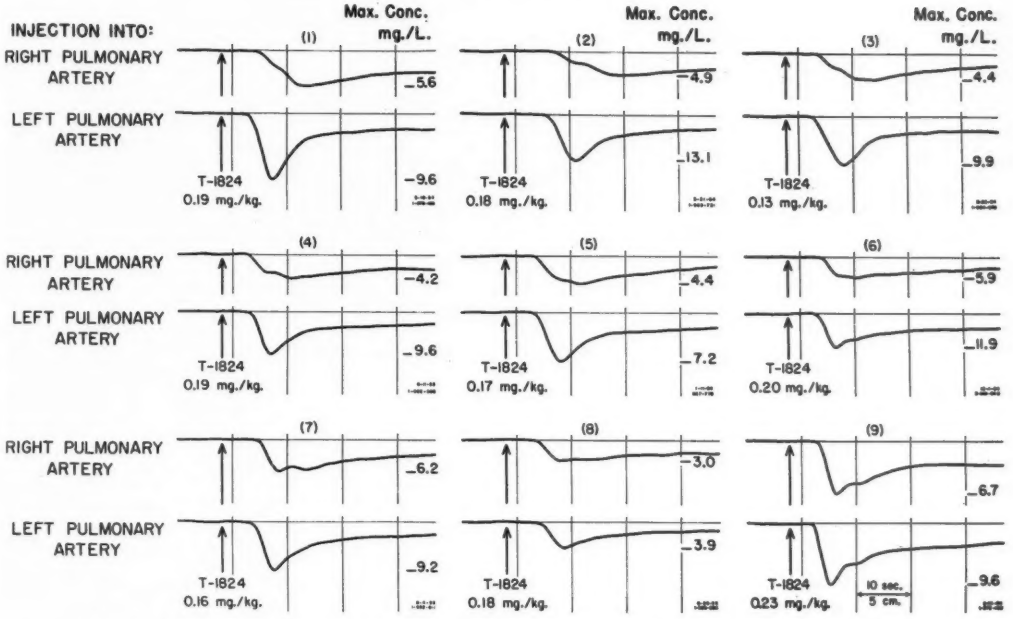


FIG. 3. Indicator-dilution curves recorded by earpiece oximeter in atrial septal defect. The number in parentheses above each pair of curves corresponds to the case number in table 1. The dose of T-1824 in each case is given below the arrow that indicates the instant of injection. See also legend to figure 2*B*.

normal with regard to both time and concentration components. The peak-concentration time in each instance differed considerably between the dilution curves. In cases 13 and 15, these values for the curves following injection into the right pulmonary artery exceeded those following injection into the left pulmonary artery by 6.0 and 4.8 sec., respectively; in case 14, the value for the curve noted after injection into the left pulmonary artery exceeded that for the right pulmonary artery by 7.5 sec. The interpretation and significance of these dilution curves are considered in detail below.

Persistent Common Atrioventricular Canal. The dilution curves obtained in 3 instances of common atrioventricular canal (fig. 6*A*) are considered in this paper because this anomaly frequently may give rise to a clinical and hemodynamic picture that is extremely difficult to distinguish from that of the usual case of atrial septal defect. The most notable feature of each of these pairs of curves was the greater degree of similarity between them as contrasted to the curves already considered. However, in cases 16 and 17 (fig. 6*B*), the initial deflections, which corresponded to a concentration of dye of 6.6 and 5.6 mg./L., respectively, produced by dye injected into the right pulmonary artery were smaller than those obtained when dye was injected into the left pulmonary artery (7.6 and 8.5 mg./L.). The dilution curves in case 18 appeared to be identical; in this respect, this case resembled those in which a ventricular septal defect or patent ductus arteriosus is present.

DISCUSSION

The features of an indicator-dilution curve are largely determined by the anatomic and dynamic conditions that pertain between the site of injection and the sampling site. The data presented can be interpreted in terms of the differing pathways traversed by the indicator from injection to sampling site and in terms of the cardiac output and the magnitude

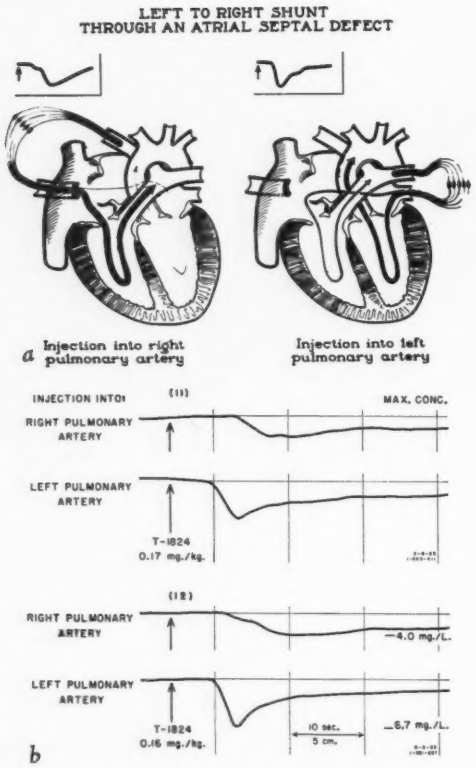


FIG. 4. *A*. Diagrammatic representation of the circulatory pathway traversed by dye in a case of atrial septal defect with "secondary" anomalous connection of the right pulmonary veins (case 12). See legend to figure 2*A* for explanatory details. Note the entry of the right pulmonary veins into the chamber of the right atrium.

B. Indicator-dilution curves obtained in 2 cases of atrial septal defect and "secondary" anomalous connection of the right pulmonary veins (cases 11 and 12). See legend to figure 2*B* for explanatory details. Values for maximal concentration are not given in case 11 because dilution curves from radial arterial blood were not obtained in this instance.

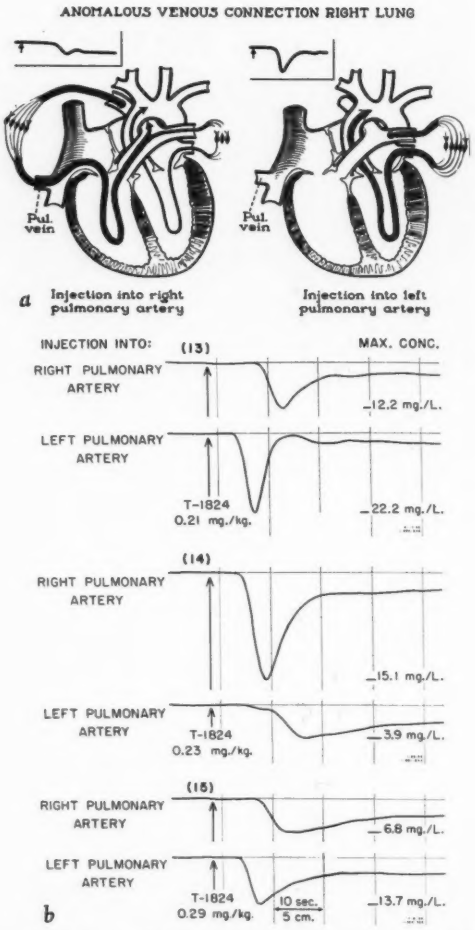


FIG. 5. *A*. Diagrammatic representation of the circulatory pathway taken by dye in a case of anomalous connection of the right pulmonary veins to the inferior vena cava and no interatrial communication (case 13). See legend to figure 2*A* for explanatory details.

B. Indicator-dilution curves in three cases of anomalous connection of the veins from one lung. The connection in cases 13 and 15 was from the right lung to the inferior vena cava, whereas in case 12 it was from the left lung to the innominate vein. See legend to figure 2*B* for explanatory details.

of recirculation of the indicator through the lungs.

The one patient who had anomalous connection of the right pulmonary veins and no interatrial communication (case 13, fig. 5*B*) provides a clear-cut example of these effects on the arterial indicator-dilution curves. The curves obtained from this patient are considered in detail to facilitate the interpretation of the findings in the other patients who had interatrial communications in which the determining factors were more complex.

When indicator dye was injected into the left pulmonary artery, a normal arterial dilution curve was recorded at the sampling site, with an appearance time of 5.0 sec., a rapid deflec-

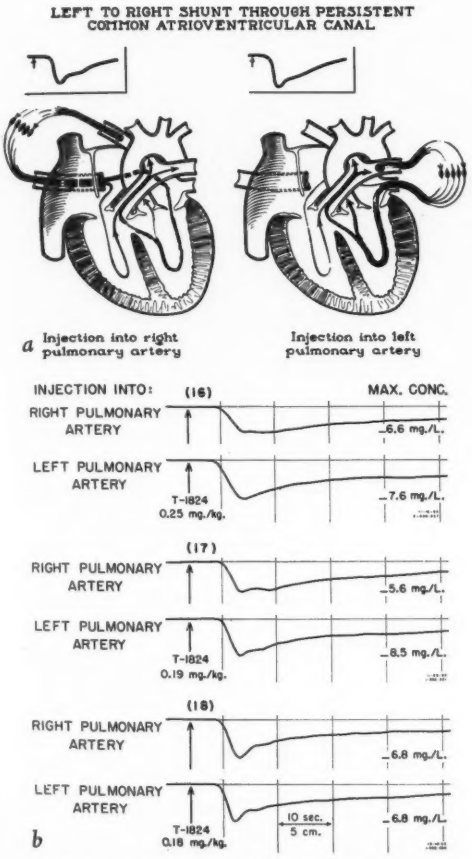


FIG. 6. *A*. Diagrammatic representation of the circulatory pathway followed by dye in a case of persistent common atrioventricular canal characterized by moderate left-to-right shunts at the atrial and at the ventricular level. The explanatory notes of the legend to figure 2*A* pertain. Note the presence of both interatrial and interventricular communications and that the right pulmonary veins are shown entering the left atrium somewhat removed from the atrial septal defect.

B. Indicator-dilution curves recorded after injection of dye in 3 cases of common atrioventricular canal. Note the rough similarity between the pairs of curves, in contrast to those in figures 2*B* and 3. However, small differences exist between the pairs of curves in cases 16 and 17.

tion to a peak of concentration at 9.0 sec. followed by a rapid decline toward 0 concentration, and a small peak of concentration 16 sec. after the main peak. In contrast, when indicator was injected into the right pulmonary artery, the appearance time was 10 seconds, the peak deflection was reduced to 12.2 mg./L., and the slope of declining concentration was prolonged.

The reason for the differences between these curves is evident on consideration of the diagrammatic representation of the central circulatory system in this patient (fig. 5*A*). Blood from the right ventricle can reach the systemic circulation only by way of the left pulmonary artery. Furthermore, all of the blood traversing the left pulmonary artery passes to the systemic circulation. Indicator injected into the anomalously connected right lung and passing to the sampling site in the arterial system traverses a path lengthened by the vascular bed of the right lung, the right atrium, ventricle, and main pulmonary artery. This results in a delayed arrival of indicator at the sampling site and hence a prolonged appearance time. In addition, only a portion (approximately 50 per cent) of the indicator that reaches the main pulmonary artery on its first recirculation from the right lung enters the left pulmonary artery; thus the magnitude of the first deflection was reduced. The remainder of the indicator again enters the right pulmonary artery and is recirculated; progressively smaller amounts (a constant fraction of the indicator remaining in the pulmonary circulation) passes to the systemic arterial system by way of the left pulmonary artery with each recirculation. This slow clearance of indicator from the central circulation caused the prolonged decline of concentration of indicator noted at the arterial sampling site. The dilution curves in this patient demonstrate that all the blood from the left pulmonary artery drained normally, while all the blood from the right lung drained anomalously. This hemodynamic situation indicated the anatomic nature of the malformation to be an anomalous connection of the right pulmonary veins, with an intact atrial septum.

Each of the remaining patients with anomalously connected veins had an associated atrial septal defect through which blood was shunting. In case 14 (fig. 5*B*) (connection of left pulmonary veins to innominate vein), the curve recorded after injection of dye into the

right pulmonary artery showed a slurring of the disappearance slope and the absence of a peak due to systemic recirculation, findings that are suggestive of a small left-to-right shunt of blood returning from the right lung. When indicator was injected into the left pulmonary artery, a small deflection coincided in time with the main deflection for the right pulmonary arterial curve, while the main deflection in the left pulmonary arterial curve was delayed by about 7 seconds. The small initial deflection in this curve was due to the presence of a right-to-left shunt through an interatrial communication, while the main deflection was due to anomalous drainage of blood from the left lung. Such an interpretation was substantiated by a dilution curve recorded after injection of dye into the superior vena cava. This curve (not shown), except for a slightly shorter appearance time, was identical to the curve noted after injection of dye into the left pulmonary artery, indicating that the blood from the left pulmonary veins drained into the superior vena cava, right atrium, or adjacent great veins. These dilution curves demonstrated, apart from the small quantity of blood shunted from right to left, the presence of complete anomalous drainage of the blood returning from the left lung; they also showed that, although the greater part of the blood returning from the right lung drained normally, a small fraction drained anomalously. This was indicative of anomalous connection of the left pulmonary veins and the presence of an atrial septal defect, with both right-to-left and left-to-right shunts occurring through it. By similar reasoning, the curves in case 15 (fig. 5*B*) were interpreted to demonstrate complete anomalous drainage of blood returning from the right lung with a moderate to severe degree of anomalous drainage of blood returning from the left lung, consistent with anomalous connection of the right pulmonary veins and an atrial septal defect.

The interpretation of the dilution curves obtained in anomalous pulmonary venous connections can be extended to include the curves in atrial septal defect. The 2 patients who had "secondary" anomalous connection of the right pulmonary veins provide a convenient transition between the groups mentioned above. The dilution curves obtained in case 11 (fig. 4*B*) are clearly similar to those of case 15 (fig. 5*B*) and were interpreted to indicate complete anomalous drainage of blood returning from the right lung associated with a considerable degree of anomalous drainage of blood returning from the left lung. Again, this finding was indicative of the anatomic diagnosis of anomalous connection of the right pulmonary veins and an atrial septal defect, a diagnosis that was substantiated at operation. Case 12 (fig. 4*B*) illustrates a less severe hemodynamic derangement in that not quite all the blood returning from the right lung drained anomalously, as depicted diagrammatically in figure 4*A*. A large atrial septal defect with a "secondary" anomalous connection to the right atrium was found in this patient at operation. Although the right pulmonary vein was connected anomalously, a small amount of blood returning from the right lung drained normally by way of the atrial septal defect. However, almost all of the blood returning from the right lung and a considerable amount of blood returning from the left lung drained anomalously. The explanation of this normal drainage of a small quantity of the blood returning from the anomalously connected right lung may be that a right-to-left shunt of blood from the right atrial chamber occurred across the atrial septal defect. Alternatively, it is possible that some of the blood returning from the right lung was shunted across the defect without having mixed with the venous blood in the right atrium. In regard to the first of these possibilities, it has been shown that small right-to-left shunts are common in cases of interatrial communication and are usually demonstrated from the inferior vena cava.[14] No right-to-left shunt of superior vena caval blood was demonstrated in this patient but, since dye was not injected into the inferior vena cava, the possibility of a right-to-left shunt from the atrium has not been excluded. Therefore, it is not possible to be certain which interpretation is correct.

The dilution curves obtained from patients with atrial septal defects had certain features in common (fig. 2*B* and 3). In every instance, the curve recorded after injection of indicator

into the left pulmonary artery was more nearly normal in contour. The initial peak of concentration was larger and the rate of declining concentration more rapid than for the curve obtained after injection into the right pulmonary artery. For the latter site, the initial peak of concentration was not the maximal concentration, which usually occurred 4 to 6 sec. later. This has been termed "peak concentration (recirculation)," abbreviated as $P.C._R$. It corresponded in time to the small break usually seen on the declining slope of concentration of the curves recorded after injection of indicator into the left pulmonary artery. For the latter site of injection, however, this peak of concentration was poorly defined at best and frequently was represented only by a change in the slope of declining concentration.

It will be recalled that total anomalous drainage of the blood from 1 lung was clearly demonstrated in 4 of the patients who had anomalous connections of pulmonary veins (cases 11, 13, 14, and 15). In the dilution curves recorded after injection of dye into the left pulmonary artery (fig. 2*A*), in the patients with atrial septal defects, the large initial deflection represented the passage of a major proportion of the injected dye to the left ventricle and to the systemic circulation after its first passage through the left lung. The small break, or slurring, on the slope of declining concentration represented dye that had been shunted from left to right through the atrial septal defect and appeared at the arterial sampling site after a second circulation through the lungs. These dilution curves indicated that a large part of the blood returning from the left lung drained normally, but that a demonstrable fraction did drain anomalously. By analogous reasoning, the small initial peaks of the dilution curves after injection of dye into the right pulmonary artery are interpreted to indicate that a small portion of the blood returning from this lung drained normally. The larger secondary peak indicated that a proportionately greater amount drained anomalously. In addition, it may be noted that the greater proportion of the blood returning from the right lung that passed to the left ventricle after its first recirculation through the lungs would probably do so by way of the left pulmonary artery.

On the basis of these dilution curves and those obtained in additional surgically proved cases of atrial septal defect, it is clear that anomalous drainage of the blood returning from the right lung, greater in magnitude than the anomalous drainage of blood returning from the left lung, is a fundamental part of the hemodynamic derangement in the *usual* case of atrial septal defect. In 2 patients with atrial septal defects, the proportion of blood draining anomalously was equal from each lung. In each of these patients, who were in the older age group, a considerable gradient in pressure was present between the atria, and at operation the defects were found to be unusually small. The probable reason for the phenomenon found in the more usual case of atrial septal defect is the anatomic proximity of the left atrial orifices of the right pulmonary veins to the defect and the relatively distant location of the orifices of the left pulmonary veins. It is reasonable to conclude that the blood returning from the left lung passing across the left atrium to the left ventricle and to the right atrium acts as a fluid stopper in regard to the blood returning from the right lung.

The demonstration of an equal contribution from each lung to a left-to-right shunt implies that intimate mixing of the blood from each lung has occurred proximal to the location of the shunt. Thus, in those cases of patent ductus arteriosus and ventricular septal defect in which dilution curves have been recorded after injection of dye into both the right and left pulmonary artery, the contours of the dilution curves indicated contributions of equal magnitude from each lung to the left-to-right shunt. Complete mixing must also be assumed to have occurred in the 2 cases with small atrial defects referred to in the preceding paragraph. This situation existed in 1 of the 3 cases of persistent common atrioventricular canal (case 18, fig. 6*B*) but the dilution curves in the other 2 cases of this anomaly indicated that a greater proportion of the blood returning from the right lung was shunted to the right side of the heart. This difference between the contribution from each lung was less than that seen in

the usual case of atrial septal defect. Of the total left-to-right shunt, a greater proportion was calculated to have occurred at the ventricular level in case 18 than in either of the other 2 cases. It is possible that the location of the interatrial communication, which is farther removed from the left atrial orifices of the right pulmonary veins, may permit a more intimate degree of mixing to occur before the streams of blood reach the defect, and may allow for anomalous drainage more nearly equal in magnitude from each lung.

The location of the tip of the catheter at the time of injection of dye is clearly of fundamental importance in determining the presence and degree of anomalous drainage from one or the other lung. The placement of the catheter in the correct position may be difficult at times, and certainty of the exact location of its tip requires radiologic confirmation before and immediately after the injection. The main trunk of each pulmonary artery is short and, in patients with increased pulmonary flow, widely dilated. The injection into either the right or the left pulmonary artery must be made close to its origin from the main pulmonary artery. This is essential because anomalous drainage of differing magnitudes has been demonstrated from the lobes of the lung in patients with atrial septal defects,[15] and in dogs with surgically created atrial septal defects.[16] Frequently, however, the longitudinal motion of the catheter induced by the heartbeat may cause the tip of the catheter to move from the right pulmonary artery into the main or even the left pulmonary artery without manipulation by the physician.

Summary

Systemic arterial indicator-dilution curves have been recorded by means of oximeters after injection of T-1824 (Evans blue) into both the right and left pulmonary artery in 12 patients who had atrial septal defects, 3 patients who had anomalous connections of the veins from 1 lung, and 3 patients who had persistent common atrioventricular canals.

The greatest differences in contour between the curves recorded after injection at these 2 sites were observed in anomalous pulmonary venous connection. The dilution curves obtained in these patients when dye was injected into the pulmonary artery of the lung that was connected normally either were normal or showed minimal abnormality. The dilution curves noted after injection of dye into the pulmonary artery of the other lung showed a significant increase in appearance time, a reduced peak of concentration and a much prolonged slope of declining concentration. The curves obtained after use of the former site of injection were interpreted to indicate normal drainage of all or nearly all of the blood returning from that lung. Those obtained after use of the latter site indicated complete anomalous drainage from the anomalously connected lung.

In the patients who had atrial septal defects, the dilution curves differed remarkably from one another. The curves obtained after injection into the left pulmonary artery were more nearly normal, but showed abnormalities of varying degree of the slope of declining concentration. After injection into the right pulmonary artery, the dilution curves were characterized by 2 peaks of concentration, the first of which was usually small in magnitude and coincident in time with the main deflection that resulted from injection of dye into the left pulmonary artery. The second deflection, usually the larger, followed the first by an interval of 4 to 6 sec. These dilution curves are interpreted to indicate a moderate degree of anomalous drainage of blood from the left lung and a severe degree of anomalous drainage of blood from the right lung. This anomalous drainage of relatively greater magnitude from the right lung appears to be a consistent feature in the usual case of atrial septal defect and is most probably a consequence of the juxtaposition of the atrial septal defect to the left atrial orifices of the right pulmonary veins.

Summario in Interlingua

Curvas de dilution de indicator in arterias systemic esseva registrate per medio de oxymetros post le injection de blau de Evans in le dextere e sinistre arterias pulmonar de 12 patientes con defectos del septo atrial, 3 patientes con anormal connexiones del venas ab un del pulmones, e 3 patientes con persistente canales atrioventricular commun.

Le plus grande differentias in le curvas

obtenite post le duo injectiones esseva observate in casos de anormal connexion pulmonovenose. Le curvas de dilution obtenite in iste patientes post injectiones del colorante in le arteria pulmonar del pulmone con connexiones normal esseva normal o monstrava grados minimal de anormalitate. Le curvas de dilution obtenite post injectiones in le arteria pulmonar del altere pulmone exhibiva un significative augmento del intervallo de manifestation, un reducite maximo de concentration, e un prolongatissime descendita del concentration. Le curvas obtenite post injectiones in le prime del sitos mentionate esseva interpretate como provas de drainage normal de omne o quasi omne le sanguine retornante ab le pulmone in question. Le curvas del secunde typo esseva interpretate como provas de drainage complete anormal ab le anormalmente connectite pulmone.

In le patientes con defectos atrioseptal, le curvas de dilution differeva remarcabilemente le unes ab le alteres. Le curvas obtenite post injectiones in le sinistre arteria pulmonar esseva plus tosto normal, sed illos monstrava varie grados de anormalitate in le branca de concentration descendente. Post injectiones in le dextere arteria pulmonar, le curvas de dilution esseva characterisate per 2 culmines de concentration. Le prime de iste culmines esseva usualmente de magnitude minor e coincideva chronologicamente con le deflexion major que resultava ab le injection de colorante in le sinistre arteria pulmonar. Le secunde deflexion, usualmente plus grande que le prime, sequeva post un intervallo de inter 4 e 6 sec. Iste curvas de dilution es interpretate como signos de un moderate grado de drainage anormal de sanguine ab le pulmone sinistre e de un sever grado de drainage anormal de sanguine ab le pulmone dextere. Il pare que iste drainage anormal de relativemente plus grande amontas de sanguine ab le pulmone dextere es un characteristica regular in le casos commun de defecto atrioseptal. Illo es probabilissimemente un consequentia del juxtaposition del defecto atrioseptal con le orificios sinistro-atrial del dextere venas pulmonar.

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Quantitative Estimation by Indicator-Dilution Technics of the Contribution of Blood from Each Lung to the Left-to-Right Shunt in Atrial Septal Defect

By H. J. C. Swan, M.B., Peter S. Hetzel, M.D., and Earl H. Wood, M.D.

A method based on the initial portion of indicator-dilution curves has been used to determine the proportion of blood from each lung which drains anomalously. The results obtained appear to substantiate the derivation and permit the expression, in numerical values, of the greater proportion of anomalous drainage of blood from the right lung in the usual case of atrial septal defect. The principal assumptions pertaining to the method are discussed in some detail.

SYSTEMIC arterial dilution curves of T-1824 have been used to demonstrate the hemodynamic derangement of "anomalous drainage" of pulmonary venous blood in certain forms of acyanotic congenital heart disease characterized by a left-to-right shunt.[1] In the usual case of atrial septal defect the proportion of blood from the right lung which drains anomalously is greater than from the left lung. This paper outlines a method for the estimation of the magnitude of the anomalous drainage from each lung.

The principal features of dilution curves obtained following injection of an indicator into the right and into the left pulmonary arteries in the usual case of atrial septal defect are evident in the example given in figure 1. The initial peak of concentrations, which occurs at 10.4 sec. and 10.0 sec. after injections of dye into the right pulmonary artery and into the left pulmonary artery respectively, is due to indicator that drains normally to the left ventricle on the first circulation. The second peak of concentration, which occurs at 14.8 sec. and at approximately 14.5 sec. following injection of indicator at each of these respective sites, represents indicator that has drained anomalously to the right atrium, and has passed, principally by way of the left pulmonary artery, to the systemic circulation following its second passage through the lungs.

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Theoretic Considerations

In the absence of mitral insufficiency, or of an interventricular or aortopulmonary communication, the cavity of the left ventricle may be regarded as a final common path, in that all of a substance which enters will pass, without delay, to the systemic circulation. For reasons that are made readily apparent in a later section, quantitative analysis which involves the determination of components of dye concentration is best confined to that part of the dilution which represents the curve of increasing concentration due to dye which passes to the systemic circulation on its first circulation. The calculation of the proportion of anomalous drainage that occurs from each lung is based on a determination of the fraction of the quantity of dye injected into the right or left pulmonary artery which reaches the left ventricle on its first circulation.

Calculation of the Blood From Each Lung Which is Shunted Left-to-right. Considering arterial dilution curves obtained in a normal subject, the equation* for the determination of cardiac output, Q_S[2], in its usual form and application is:

$$Q_S = \frac{60\ I}{\bar{C} \cdot T_P} \qquad (1)$$

in which I is the quantity of indicator in mg., T_P is the passage time in sec., $\bar{C}$ is the average concentration in mg./L. and Q_S is the systemic

* The symbols used have been defined in a previous publication.[3]

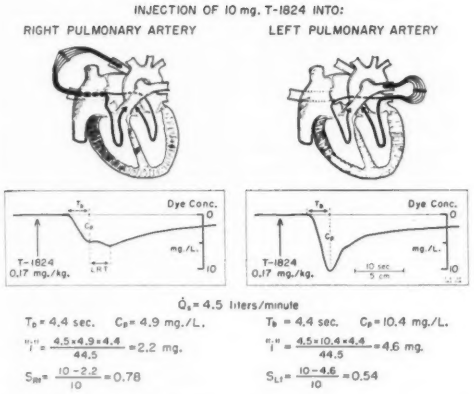

FIG. 1. The calculation of the magnitude of the left-to-right shunt from each lung in a patient with an atrial septal defect (case 10). In the upper panel the circulatory paths taken by indicator injected into the right and into the left pulmonary artery are represented. Beneath each diagram the dilution curves obtained in case 10 are depicted for the respective injection sites. Symbols as used in text. Beneath each dye curve are calculations of i (using equation 5) and of S_R and S_L (using equation 6) based on T_b, C_p, and $\dot{Q}_S$.

blood flow in L./min. The estimation of Q_S requires the determination of values for $\bar{C}$ and T_P from a dilution curve, excluding the effect of recirculated indicator.

It has been found that the initial portion of a dilution curve may be represented with some accuracy by a triangle of which the base is the build-up time, T_B, and the altitude is the peak concentration C_P.[4] The area of this triangle ($\frac{1}{2}T_B \times C_P$) bears a relatively constant relation to the total area of the curve. In a series of 36 curves from subjects who did not have abnormal circulatory paths, the ratio of the area of the initial triangle to the area of the total curve was 0.37.

This relationship may be expressed as

$$\bar{C} \cdot T_P = \frac{\frac{1}{2}C_P \cdot T_B}{0.37} . \qquad (2)$$

Substituting for $\bar{C} \cdot T_P$ in equation 1,

$$Q_S = \frac{60\, I \cdot 0.37}{\frac{1}{2}C_P \cdot T_B} . \qquad (3)$$

Solving for I this becomes

$$I = \frac{Q_S \cdot C_P \cdot T_B}{2 \cdot 60 \cdot 0.37} = \frac{Q_S C_P T_B}{44.5} . \qquad (4)$$

The dilution curve seen in the presence of a left-to-right shunt may be considered as having in its initial portion a dilution curve of normal contour due to that indicator which has reached the left ventricle on its first circulation, on which is superimposed further concentration changes due to recirculated indicator. If no recirculation were present, the magnitudes of the time and concentration components of the dilution curves would be functions of the systemic flow and the quantity of dye injected into the central circulation, all of which reaches the left ventricle. In the same manner, a relationship will exist between the systemic blood flow, Q_S, the components of the *initial* part of the dilution curve (if no recirculated indicator obscured its dimensions) and the quantity of dye entering the left ventricle. Designating this quantity i, equation 4 may be rewritten in terms of the initial dilution curve prior to its peak of concentration.

$$i = \frac{Q_S \cdot C_p \cdot T_b}{44.5} . \qquad (5)$$

In this equation, C_p and T_b pertain to the abnormal dilution curve. Equation 5 contains 2 unknown terms, i and Q_S, while values for C_p and T_b can be measured from the recorded dilution curve (fig. 2). If agreement is assumed between estimates of systemic flow by indicator-dilution technics and by the Fick method, a value for Q_S, the systemic blood flow, determined by the latter estimate may be used to permit solution of equation 5 in terms of i. This value represents the number of milligrams of dye which, under these conditions, entered the left ventricle in order to produce a dilution curve with the observed values of C_p and T_b. The assumptions underlying the use of these values are discussed in a later section.

Since i represents the quantity of dye that enters the left ventricle and hence drains normally, then, if I_o is the total quantity of dye injected, $I_o - i$ = quantity of dye draining anomalously and

$$\frac{I_o - i}{I_o} = S_R \text{ or } S_L \qquad (6)$$

where S_R or S_L represents the fraction of dye, shunted from left to right through the defect, in the blood returning from the right or left lung

following injection of dye into the right or left pulmonary artery. If uniform mixing of dye and blood is assumed, this equals the fraction of blood draining from the respective lungs to the right atrium.

If the assumption is also made that, of the total volume of blood flowing through both lungs, 48 per cent traverses the left lung, and 52 per cent the right lung,[5] then the proportion of the pulmonary blood flow, S, which drains anomalously is given by the equation

$$S = 0.48\ S_L + 0.52\ S_R \qquad (7)$$

in which S equals the total left-to-right shunt as a fraction of the total pulmonary flow.

Calculations of Mean Pulmonary Recirculation Time and Pulmonary Blood Volume. The systemic arterial dilution curves recorded following injection of indicator into the right pulmonary artery were characterized by the presence of 2 peaks of concentration. Each of these peaks represents a maximal concentration of indicator—the first, that due to indicator passing directly to the left ventricle—the second, that due to indicator which had recirculated through the pulmonary vascular bed before entering the left ventricle. The interval between these peaks has been designated the "lung recirculation time" (LRT). A precise definition of this interval in terms of velocities, vascular path lengths and quantities of indicator is not attempted here. In general terms, the interval would appear to be related to the time taken by the average particle to traverse the pulmonary vascular bed. Adapting the formula of Hamilton and associates[6] and using the value LRT as a mean pulmonary circulation time, the volume of blood in the lungs was calculated:

$$PBV = \frac{LRT \times Q_P}{60 \times W}\ . \qquad (8)$$

If Q_P is the pulmonary blood flow in ml./min. (see later), W is body weight in kilograms and LRT is given in sec., then PBV is the pulmonary blood volume in ml./Kg. Theoretically, the value so derived will have the same relation to the true volume of blood within the heart and lungs as the LRT bears to the mean pulmonary circulation time.

Methods

Each patient was studied by the cardiac catheterization procedure. As outlined previously,[1] arterial indicator-dilution curves following injection of T-1824 into the right and into the left pulmonary artery[7] while the patient breathed 100 per cent oxygen were recorded by means of oximeters fastened to each ear, and simultaneously by means of a cuvette oximeter[8] through which blood from the radial artery was allowed to flow. Since it was possible to calibrate the deflection produced by the cuvette oximeter in regard to concentration of T-1824, the dilution curves recorded utilizing this instrument are the basis for the data in this report. The dilution curves recorded by means of the ear oximeter have been reproduced for each patient previously. The numerals used refer to the same patients in each paper. Quantitative data were not obtained in case 11.[1]

The pulmonary, Q_P,* and systemic, Q_S, blood flows were calculated (in L./min.) from the equations:

$$Q_P = \frac{VO_2}{C_{PVO_2} - C_{PAO_2}}$$

$$Q_S = \frac{VO_2}{C_{SAO_2} - C_{MVBO_2}}$$

in which VO_2 is the value for oxygen consumption in ml./min., and C_{PVO_2}, C_{PAO_2}, C_{SAO_2} and C_{MVBO_2} represent the oxygen content (ml./L.) of the pulmonary vein blood, pulmonary artery blood, systemic artery blood, and mixed venous blood, respectively. The value for C_{PVO_2} while the patient breathed 100 per cent oxygen was taken to be equal to C_{SAO_2} and was found to exceed the oxygen capacity of arterial blood by 1.8 ml./100 ml. of blood in every instance. Values for C_{PAO_2} and C_{SAO_2} were determined by the method of Van Slyke. The value for C_{MVBO_2} was determined by the relationship

$$C_{MVB} = \frac{2\ C_{IVC} + C_{SVC}}{3}$$

where C_{IVC} and C_{SVC} represent the oxygen content of inferior and superior vena cava blood respectively. Assuming no right-to-left shunt of significance to be present, the percentage of left-to-right shunt was calculated:

$$L\text{-}R \text{ shunt} = \left(\frac{Q_P - Q_S}{Q_P}\right) \times 100. \qquad (9)$$

Results

Patients with Atrial Septal Defect. In the 11 patients with atrial septal defect the pulmonary

* Symbols modified from Pappenheimer and associates.[9]

blood flow as measured by the Fick principle averaged 17.8 L./min. (range 9.6 to 27.0 L./min.). No patient had demonstrable arterial desaturation. The proportion of left-to-right shunt averaged 70 per cent (range 55 to 81 per cent). The indicator-dilution curves recorded following injection of T-1824 into the right pulmonary artery had average appearance and build-up times of 6.7 and 4.2 sec. Following injection into the left pulmonary artery, these values were 6.1 and 4.6 sec., respectively. The average peak concentration time for the curves recorded following injection at the former site was 10.9 sec. and at the latter injection site was 10.7 sec.

Using equations 5 and 6, the proportion of the blood traversing the right lung that drained anomalously (shunted from left to right) averaged 84 per cent (range 75 to 97 per cent), and of the blood traversing the left lung an average of 54 per cent (range 35 to 75 per cent) drained anomalously. The proportion of the total volume of the blood that drained anomalously, calculated by means of equation 7, had an average value of 70 per cent (range 63 to 80 per cent). The relation between this value calculated by means of the indicator-dilution curves (equation 7) and the value obtained by using the estimates of pulmonary and systemic blood flow (equation 9) is shown in figure 2. The average of the difference between the values determined by each of these methods was 0 and the standard deviation of these differences was 6.6 per cent. The proportion of the blood which drained anomalously, having traversed the right lung, exceeded that which drained anomalously after traversing the left lung in every instance. The average difference was 31 per cent with a wide variability (8 to 61 per cent). A consistent relationship between this difference and the magnitude of the shunt could not be demonstrated.

The "lung recirculation time" (LRT) was found to average 4.4 sec. (range 3.2 to 5.5 sec.). The volume of blood in the heart and lungs was determined according to equation 8. The average value was 23 ml./Kg. (range 12 to 36 ml./Kg.). The roentgenograms of the chest of every patient, except for patient 12, were

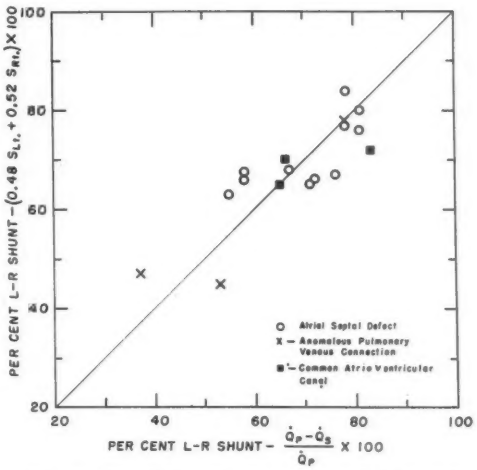

FIG. 2. The relation between the magnitude of the left-to-right shunt in 17 patients calculated from the flow values (equation 9) and on the bases of the dye-dilution curves obtained following injection of T-1824 into right main and into left main pulmonary artery (equations 5 and 7).

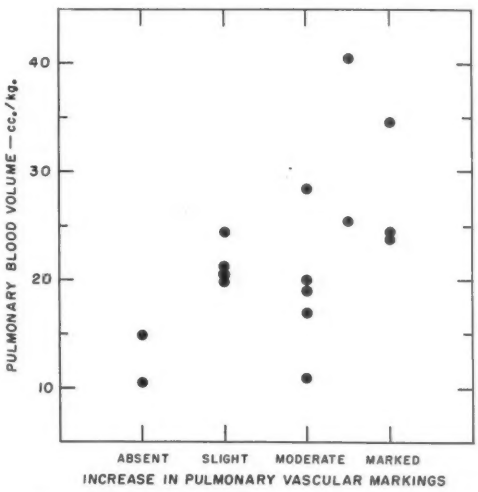

FIG. 3. The relation between the increase in pulmonary vascular marking (radiologic grading) and the estimated pulmonary blood volume (equation 8).

graded according to the prominence of the pulmonary vascular markings by Dr. André Bruwer of the Section of Diagnostic Roentgenology. The relation between this grading and the values obtained by equation 8 is shown in figure 3. Except for patient 7, in whom other

abnormal findings were minimal, the agreement obtained was satisfactory.

Patients with Anomalous Pulmonary Venous Connection or with Persistent Common Atrioventricular Canal. The relevant data for these patients are given in the table.

In case 13, in which no left-to-right shunt had occurred from the left lung, the calculation based on the dye-dilution curve indicated a loss of 5 per cent of the dye that had been injected into the left pulmonary artery. In case 14, it was calculated that 15.9 mg. of T-1824 were required to produce the dilution curve recorded following injection of indicator into the right pulmonary artery (which was the artery supplying the normally connected lung in this instance). However, only 15 mg. of T-1824 had been injected, and an error known to be in excess of 6 per cent resulted. Calculations based on the dilution curves in case 15 showed good agreement between the magnitude of the shunt as determined by the dye method and from the flow values.

In the patients with persistent common atrioventricular canal, the calculations supported the impression, based on inspection of the curves, that the proportion of anomalous drainage from each lung was more nearly equal than in many cases of atrial septal defect. In 2 of the cases of atrial septal defect presented in this paper, this difference in the proportion of blood draining anomalously from each lung was equally small, but each of these patients had pulmonary recirculation of a more severe degree.

Discussion

This paper represents an attempt to express in quantitative terms a phenomenon that may be qualitatively deduced by inspection of indicator-dilution curves in patients with atrial septal defect. It is justified only if the principal assumptions are reasonable, and if the values derived thereby do not deviate substantially from estimates of the same quantities by other accepted methods. This discussion is confined to a consideration of the quantitative method, the more qualitative implications having already been presented in detail.[1]

The estimation of pulmonary, Q_P, and systemic, Q_S, blood flow is first to be considered The oxygen content of blood samples from the inferior vena cava and superior vena cava is utilized to calculate C_{MVBO_2}. Any inaccuracy in these values will cause an error in Q_S. However, when the difference $(C_{SAO_2} - C_{MVBO_2})$ is considerable, small errors in either C_{SAO_2} or C_{MVBO_2} are of minor significance. Concerning Q_P, errors of significance appear more likely. Although only small absolute errors are likely in the estimation of C_{PVO_2} and C_{PAO_2}, an error of considerable magnitude is possible when the difference $(C_{PVO_2} - C_{PAO_2})$ is small. This potential error is reduced in expressing the relative magnitude of the left-to-right shunt as a ratio

$$\frac{Q_P - Q_S}{Q_P}.$$

Agreement between estimates of systemic blood flow by the dye-dilution method and by the Fick method have been reported by several investigators[10, 11] and is not discussed further here. The standard deviation of differences between these methods found in this laboratory was ± 16 per cent.[11] There is also general agreement as to the division of the total volume of the pulmonary blood flow, so that approximately 52 per cent traverses the right lung and 48 per cent traverses the left lung.[5] This division is related to the total quantity of lung tissue that comprises each lung, and, since it has been found to hold during exercise,[5] it appears likely to apply also in the presence of pulmonary recirculation. Even moderate deviations from these relative proportions will affect the principal calculations but little.

The data of Hetzel and associates[4] relate the value $(C_P \times T_B)$ to the total area subtending the dilution curve obtained in normal subjects and in patients without an intracardiac shunt, the effect of indicator that has traversed the systemic capillaries having been eliminated. The variability of this relation over a wide range of values of systemic blood flow was sufficiently small to enable the total area of the dilution curve to be predicted with considerable accuracy from the values for C_P and T_B. Further, in 4 normal dilution curves recorded following injection of indicator into the left ventricle or aorta, the relation of $(C_P \times T_B)$ to

the total area of the curve (excluding the effect of systemic recirculation) was similar.

The quantitative application of indicator-dilution technics in the presence of pulmonary recirculation due to an interatrial communication is now considered. Clearly, many additional assumptions pertaining to the use of these technics, as outlined by Hamilton and associates,[6] Zierler,[12] and others, are implicit in the following paragraphs, in which those aspects that appear most relevant to the present problem are presented.

Adequacy of Mixing. Following injection of indicator into the right or the left pulmonary artery, it is assumed that the dye is representatively mixed with the blood traversing the respective lung. In practice, this may not always be attained because of difficulty in avoiding a selective injection of indicator into one or other of the branches of the right or left pulmonary artery. In some patients significant differences have been demonstrated between the drainage of blood from the upper, middle, and lower lobe pulmonary veins, in particular from the right lung. However, in the few instances in which a repeat injection of indicator has been made into a main pulmonary artery, closely similar curves have been obtained.

Determination of T_b. The instant at which indicator is first recognized at the sampling site, t_a,* is clearly one of the determinants of T_b. A finite concentration of indicator is necessary for recognition. Further, at any instant the concentration is a function of the total quantity of indicator that has entered the left ventricle on its first circulation. Thus, the instant at which the minimal detectable concentration of indicator can be recognized is in part dependent on the proportion of blood that drains normally. It is possible that when small quantities of indicator enter the left ventricle the true instant of appearance, t_a, may not be recognized and an error in determination of T_b may result. For the 11 patients with atrial septal defect considered in this paper, the average peak concentration times for the dilution curves recorded following injection of indicator into the right and into the left pulmonary artery were 10.9 and 10.7 sec., and the values for T_b were 4.2 and 4.6 sec., respectively. In several patients the differences between the value of T_b for each of these injection sites were considerable (table 1). Where this was the greatest (case 3), the magnitude of S_{Rt} was recalculated on the basis of the greater value of T_b (that is, T_b for the left pulmonary artery curve). The value for S_{Rt} declined from 89 per cent to 85 per cent, a relative error of 4.7 per cent. When applied to the calculation of the proportion of blood draining normally, this substitution in the value of T_b resulted in an increase from 11 to 15 per cent, a relative error of 27 per cent.

The instant of peak concentration, t_p, is the second determinant of T_b. The clear identification of a peak of concentration due principally to that indicator which had drained normally was possible in every instance. The influence of recirculated indicator on the position in time of this peak is probably small, for a decline in concentration following the initial peak was usually seen before the further increase in concentration due to recirculated indicator had occurred (fig. 1). Further, the peak concentration time, PCT, from the right lung was not significantly longer than from the left lung, even in those patients in whom the proportion of the blood draining anomalously differed greatly.

Determination of C_p. The initial peak of concentration of indicator is taken to represent only that quantity of indicator which drains normally, and is used in equation 5 as the value for C_p. Since the average pulmonary recirculation time has been shown to be of the same order of magnitude as the average build-up time, this assumption needs further examination. First, inspection of the majority of curves recorded following injection of dye into the *left* pulmonary artery indicates that a relatively small quantity of dye is draining anomalously, since the change in concentration due to recirculated indicator appears only as a small deformation on the slope of declining concentration. In this instance, the absolute quantity and the relative proportion of recirculated indicator that distorts the initial

* The use of lower case t refers to instants of time, while capital T refers to intervals of time.[3]

TABLE 1.—*Pulmonary and Systemic Blood Flows. Proportion of Anomalous Drainage from Each Lung and Estimates of Pulmonary Circulation Times in Patients with Atrial Septal Defect, Anomalous Pulmonary Venous Connection and Persistent Common Atrioventricular Canal*

Case	Blood flow values, L./min.		Shunt L-R. %	Right lung					Left lung					Total shunt (both lungs), %	Circulation time sec.		Pulmonary blood volume, ml./Kg.
	Pul.	Sys.		Circulation time sec.		mg./L. C_p	mg. i	Proportion of shunt (S_R), %	Circulation time sec.		mg./L. C_p	mg. i	Proportion of shunt (S_L), %		PCT_r*	LRT*	
				AT*	BT*				AT*	BT*							
Atrial septal defect																	
1	16.3	6.9	58	8.6	2.8	1.8	0.79	92	6.2	4.4	9.6	6.5	35	65	16.0	4.6	24
2	16.5	3.9	76	6.3	5.7	2.9	1.4	86	4.1	4.8	13.1	5.6	44	66	16.5	4.5	23
3	17.9	5.1	71	4.7	3.3	2.1	1.0	90	5.4	5.8	9.9	6.5	35	69	12.1	4.1	17
4	18.5	4.3	78	5.9	3.5	2.8	0.9	91	6.2	4.2	9.6	4.0	60	76	14.3	4.9	23
5	14.8	6.7	55	8.1	4.6	3.3	2.3	77	8.6	5.1	7.2	5.3	47	62	17.9	5.2	21
6	18.0	5.0	72	5.5	4.0	5.7	2.5	75	3.9	3.6	11.9	4.8	52	64	12.7	3.2	20
7	9.6	4.0	58	9.0	5.0	5.7	2.5	75	8.2	5.2	9.2	4.3	57	66	18.6	4.6	12
8	27.0	5.0	81	7.2	5.6	2.7	1.7	83	7.1	5.6	3.9	2.5	75	79	17.0	4.2	34
9	18.6	3.3	81	5.7	4.0	6.7	2.0	80	5.8	4.0	9.6	2.8	72	75	13.3	3.6	24
10	13.2	4.5	67	5.8	4.4	4.9	2.2	78	5.8	4.4	10.4	4.6	54	65	14.6	4.0	15
12	25.5	5.6	78	6.7	3.0	0.7	0.3	97	6.1	3.7	6.7	3.1	69	83	15.2	5.5	36
Anomalous pulmonary venous connection																	
13†	8.2	5.3	37	—	—	—	—	100	6.3	3.6	22.2	9.5	5	46	15.9‡	6.0	11
14	12.9	6.1	53	11.8	7.7	15.1	15.9	0	—	—	—	0	100	48	25.6‡	6.5	22
15	19.2	4.3	78	—	—	—	—	100	5.2	3.6	13.7	4.8	52	77	15.5‡	6.7	41
Persistent common atrioventricular canal																	
16	22.5	3.7	83	5.2	3.8	6.6	2.1	79	6.1	5.8	7.6	3.6	64	71	11.8	2.8	26
17	13.6	4.7	66	6.6	4.4	5.6	2.6	74	5.4	3.8	8.5	3.5	65	69	15.0	4.0	18
18	16.3	5.7	65	6.9	3.6	6.8	3.1	69	7.4	4.0	6.8	3.4	66	67	14.7	4.2	20

* AT = appearance time. BT = build-up time. PCT_r = peak concentration time including recirculation. LRT = lung recirculation time.

† Agenesis of upper lobe of right lung. Calculations based on the assumption that of the blood flowing into the main pulmonary artery 42 per cent traverses the right lung and 58 per cent the left lung.

‡ The value for PCT_r used in these cases is the interval between the instant of injection and the instant of peak concentration (which is the first peak) following injection of indicator into the artery of the anomalously connected lung.

peak of concentration is also likely to be small. Second, when the initial deflection itself is small, as in about half of the dilution curves recorded following injection of dye into the *right* pulmonary artery, it is readily apparent that no great quantity of recirculated indicator is passing to the sampling site. It could well be argued that a relatively large proportion of recirculated indicator is contributing to this initial peak. However, the slight decline in concentration which usually follows this peak implies that for this short period the concentration of indicator which has drained normally is diminishing more rapidly than the concentration due to recirculated indicator is increasing. Since the build-up slope of a normal dilution curve is more rapid than the slope of declining concentration, this suggests that the contribution of recirculated indicator to C_p may not be great in this type of dilution curve.

A greater possibility of error in applying the value C_p in equation 5 arises when the initial peak of concentration is intermediate in magnitude, and approximately equals the first peak of concentration due to recirculated

indicator. The considerations outlined in previous paragraphs regarding the significance of a definite decline or plateau of concentration following the initial peak suggest that the effect of recirculated indicator may not be excessive if the "lung recirculation time" is 4.5 sec. or greater. When this interval is short, as in case 16, for example, the contribution of recirculated indicator to the initial peak of concentration is probably considerable.

In each of the instances discussed in the preceding paragraphs, the effect of recirculated indicator is to increase the concentration of indicator assumed to represent the indicator draining normally—and results in a falsely low value for the magnitude of the proportion of indicator draining anomalously. The direction of this error is opposite to that which may result from an underestimate of T_b.

When a comparison was made between the values for the proportion of pulmonary blood shunted based on the indicator-dilution curves and the values obtained by the application of the Fick principle, a satisfactory correlation was obtained. The use of the same estimate of systemic blood flow in each determination does not appear to invalidate the significance of this comparison. The agreement found is the principal justification for the conclusion that the values obtained based on the indicator-dilution curves reflect the proportion of blood draining anomalously from each lung with a reasonable degree of accuracy—possibly of the same order as estimates of systemic blood flow by the Fick and by the dye-dilution methods.

It is perhaps of academic interest that a calculation of the proportion of the blood draining anomalously from each lung can be attempted with apparent success. The expression of a result in numerical values, however, has certain practical advantages in regard to the presentation of definitive data. Examination of certain of the assumptions that have had to be made indicates the problem of quantitative interpretation of concentration curves that may be distorted by the presence of recirculated indicator. Quantitative measurements based on concentration values following the initial peak can include several components—that due to dye which has drained normally, and those components due to dye which has recirculated through the lungs 1 or more times. It would appear that of methods of analysis based on the later portion of such dilution curves those of an empirical nature depending on relationships such as the disappearance time—build-up time ratio would be of most value.[13]

Summary

A method of analysis of indicator-dilution curves in cases of anomalous drainage of pulmonary vein blood has been derived whereby the proportion of the blood from each lung that drains anomalously may be calculated. The method utilizes measurements of build-up time and peak-concentration due to dye that drains normally, and an independent estimate of systemic blood flow. In atrial septal defect the proportion of blood draining anomalously from right and left lungs averaged 84 and 54 per cent respectively. The sums of these values agreed well with estimates of left-to-right shunt by the more conventional method $\left(\frac{Q_P - Q_S}{Q_P}\right)$. The standard deviation of the differences between the methods was 7 per cent.

Estimates of lung recirculation time (average 4.4 sec.) indicated a very rapid pulmonary circulation in many patients. Values for pulmonary blood volume in these patients were 1.0 to 2.5 per cent of body weight in most instances.

Summario in Interlingua

Esseva disveloppate un methodo pro le analyse de curvas de dilution de indicator in casos de anormal drainage de sanguine pulmono-venose, permittente le calculation de proportion de sanguine veniente ab le pulmones individual. Le methodo utilisa mesurationes del tempore accumulatori e del concentration maximal de colorantes a drainage normal insimul con un estimation independente del fluxo de sanguine systemic. In le presentia de defecto atrio-septal, le proportion de sanguine effluente de maniera anomale ab le pulmones dextere e sinistre amontava, respectivemente, a valores medie de 84 e 54 pro cento. Le summa del valores esseva ben de

accordo con le proportion $(Q_P - Q_S)/Q_P$. Le deviation standard del differentias esseva 7 procento.

Estimationes del tempore de recirculation pulmonar (valor median 4,4 sec) indicava in multe patientes un rapidissime circulation pulmonar. Valores pro le volumine del sanguine pulmonar in iste patientes esseva in le majoritate del casos 1,0 a 2,5 pro cento del peso corporee.

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What we call sense or wisdom is knowledge, ready for use, made effective, and bears the same relation to knowledge itself that bread does to wheat. The full knowledge of the parts of a steam engine and the theory of its action may be possessed by a man who could not be trusted to pull the lever to its throttle. It is only by collecting data and using them that you can get sense. One of the most delightful sayings of antiquity is the remark of Heraclitus about his predecessors—that they had much knowledge, but no sense.—WILLIAM OSLER. *The Student Life. Farewell Address to American and Canadian Medical Students.* Med. News (N. Y), 1905.

Antidiuresis and Other Renal Responses to Piperoxan in Pheochromocytoma

By A. C. Corcoran, M.D., Harriet P. Dustan, M.D., and Irvine H. Page, M.D.

The clinical recognition of pheochromocytoma as a cause of hypertension is still a difficult problem for which the many tests that have been devised are at times inadequate. In this article an antidiuretic response to piperoxan in patients with pheochromocytoma is described. In view of the diuretic response of patients without pheochromocytoma, measurement of urinary flow after injection of piperoxan is suggested as a possible simple, confirmatory guide in diagnosis.

IN NORMAL man infusions of epinephrine or norepinephrine tend to promote excretion of dilute urine at normal or increased rates of flow; the urine flow decreases sharply when the infusions are withdrawn.[1] The present report describes an analogous antidiuresis observed in patients with functioning pheochromocytoma in whom sudden partial withdrawal of adrenal medullary hormone was simulated by giving piperoxan (benzodioxane, 933 F). Concurrent changes in other renal functions are also described. The responses to the drug are compared with those found in patients without functioning pheochromocytoma, from 2 of whom such tumors had been removed, and 6 of whom showed arterial hypertension at the time of the study.

In comparison with the many careful observations of the effect of this drug on arterial pressure[2, 3] its effects on renal function have received scant attention. Further, the observations indicate that the response of urine flow to administration of piperoxan may be a useful confirmatory observation in the diagnosis of pheochromocytoma.

Methods

The study is based on measurements of plasma clearances of para-aminohippurate at low plasma concentrations (C_{PAH}) and mannitol (C_M), urine flow (V), and arterial pressure by brachial auscultation (*B.P.*). The patients were not especially prepared except that both tests in patient no. 7 were made after hydration by infusion of 1.5 L of 1 per cent NaCl over the 2 hours prior to the tests. Mannitol and PAH were given intravenously by infusion,[4] after administration of priming doses. Urine was collected by catheterization and bladder washing at intervals of about 10 min. The rate of urine flow (V) was taken as the difference between measured volume of urine plus wash and volume of bladder wash, divided by the duration of the period in minutes. The observation in patient no. 9 differs in that PAH was given subcutaneously and mannitol was not given; changes of glomerular filtration rate in this patient were estimated from measurements of endogenous creatinine clearance (C_{Cr}),* and periods of urine collection were extended over 30 min. Creatinine was measured by the method of Miller and Miller.[5]

The 4 patients with uncomplicated essential hypertension, 1 with hypertension due to acute glomerulonephritis, and patient no. 10 with functioning pheochromocytoma were each given 20 mg. of piperoxan intravenously over 1 to 3 min. at the end of the third urine collection; urine collections were then carried on for another 2 periods. Blood pressure was measured repeatedly prior to and following the injection; the values listed (table 1) are averages of 3 to 5 measurements made during each interval of urine collection. The patient with persistent hypertension after removal of a functioning pheochromocytoma (no. 6), the patient who attained normotension after removal of a pheochromocytoma (no. 7), and patient no. 8 with functioning pheochromocytoma were each observed during 3 control periods and 3 test periods and piperoxan was given during the test periods in repeated doses; in patient no. 9 the drug was infused intravenously at a steady rate of 2 mg./min.

Thus, the group studied consists of 7 "controls," including the postoperative observation of pheochromocytoma in patients no. 7 and 4. Clinical

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* C_{Cr} is not accepted as the equivalent of glomerular filtration rate, but over brief periods, changes in C_{Cr} can be assumed to result from corresponding changes in glomerular filtration rate.

TABLE 1.—*Effect of Piperoxan on Renal Functions*

Urine volume (Urine V) plasma clearances of PAH (C_{PAH}) and mannitol (C_M) and averages of arterial pressure in successive periods of about 10 minutes urine collection before and after administration of piperoxan. Patients nos. 1 to 4 inclusive were under treatment for essential hypertension and no. 5 for acute hemorrhagic glomerulonephritis.

Patient No.	Dose mg.	Time min.	Urine V	C_{PAH}	C_M	B.P. mm.Hg	R
			ml./min./1.73M.²				
A. Controls							
1		10	1.6	—	—	205/105	—
		10	1.4	475	92	210/110	.32
		10	1.4	415	85	210/110	.37
	20*	10	1.5	507	99	228/112	.33
		10	1.1	495	95	220/115	.32
2		11	1.1	419	84	180/125	.35
		10	2.3	333	82	185/125	.45
		10	2.1	336	82	188/120	.49
	20	10	2.0	304	79	190/130	.50
		10	4.2	271	78	190/120	.55
3		10	2.9	773	130	200/115	.20
		10	2.9	677	120	200/118	.22
		10	3.8	740	134	196/115	.20
	20*	10.5	4.1	752	150	200/130	.21
		10	4.2	524	106	200/130	.30
4		10	2.1	588	105	184/105	.24
		11	1.6	481	94	185/105	.29
		12	—	—	—	182/100	—
	20*	13	4.0	323	66	190/102	.44
		11	2.3	444	88	195/105	.32
5		10	2.0	622	78	165/110	.21
		10	1.6	431	75	158/108	.30
		10	2.2	375	78	152/108	.33
	20*	11	3.0	477	84	168/105	.30
		10	3.8	563	83	174/132	.26
B. Pheochromocytoma: Postoperative							
6		11	8.2	243	62	190/110	.59
		10	9.0	317	78	190/110	.46
		10	7.6	253	65	196/110	.58
	2/min.	10	9.2	318	81	196/112	.47
	2/min.	10	9.8	296	76	198/112	.51
	2/min.	10	11.2	288	72	194/108	.51
7		11	0.7	466	83	124/78	.21
		10	0.6	472	86	126/84	.21
		11	0.6	455	81	126/86	.20
	14	13	1.9	491	93	138/82	.22
	10	11	3.5	463	99	140/90	.24
	6	12	7.6	406	98	148/94	.29

TABLE 1.—*Continued*

Patient No.	Dose mg.	Time min.	Urine V	C_{PAH}	C_M	B.P. mm.Hg	R
			ml./min./1.73M.²				
C. Functioning Pheochromocytoma							
7		11	1.4	—	115	178/108	—
		11	1.8	356	103	170/102	.37
		11	1.8	326	101	168/106	.40
	14	12	0.8	526	98	164/83	.23
	10	11	0.4	646	100	169/97	.20
	16	12	0.4	665	90	138/80	.16
8		10	2.4	648	127	210/130	.25
		10	2.0	491	104	188/126	.31
		10	1.8	534	102	220/146	.33
	20	11	0.7	577	95	182/110	.24
	12	11	0.9	577	84	182/110	.24
	7	12	0.5	664	87	167/105	.20
9		30	3.1	300	54†	200/98	.48
		30	4.2	285	41†	204/100	.53
	2/min.	30	1.2	317	39†	160/90	.38
		30	0.1	410	41†	140/62	.22
10		10	2.5	640	144	228/150	.29
		13	6.9	—	—	230/158	—
		12	7.1	620	140	288/152	.35
	20*	11	0.95	553	89	192/130	.28
		13	2.15	584	84	212/140	.29

* Indicates instantaneous intravenous injection of piperoxan at the start of the period of urine collection.

† Indicates that endogenous creatinine clearance was measured as an approximation of plasma mannitol clearance.

records of patients no. 1 to 5 inclusive are not abstracted, since the findings in these cases were not remarkable; however, brief abstracts of data from the patients with pheochrome tumors are appended. Except as otherwise noted, measurements of tissue catechols were made by the iodine method of von Euler and Hamberg[6] and confirmed by bioassay in sensitized dogs and cats. Urinary catechols were similarly measured in patients no. 6, 7, and 8.

RESULTS

Results are summarized in table 1 and in figures 1 and 2; figure 3 is a graph of preoperative and postoperative observations in patient no. 7.

Controls. In the patients without functioning pheochromocytoma single injections (no. 1 to 5), infusion (no. 6), or repeated small injections

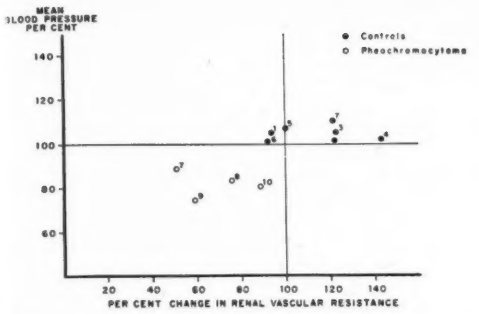

FIG. 1. Effects of piperoxan on means of blood pressure and renal resistance expressed as per cent of means of control observations.

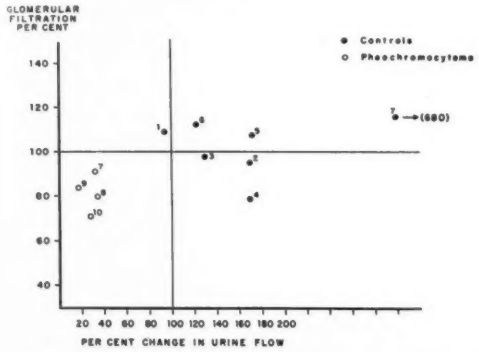

FIG. 2. Effects of piperoxan on means of glomerular filtration and urine flow expressed as per cent of means of control observations.

(no. 7) of piperoxan consistently provoked small increases of arterial pressure; averages of total renal vascular resistance (R = mean of systolic and diastolic pressures $- 5 \div C_{PAH}$) increased slightly in 4 and was unchanged in 3 (fig. 1); glomerular filtration rate (C_M) was decreased in 1 patient, unchanged in 2, and increased by about 10 per cent in 4 (fig. 2); urine flow (V) was almost unchanged in 1 and was increased in 6 patients, including no. 4, whose filtration rate was decreased; the diuresis was most intense in no. 7, in whom urine flow was increased nearly sevenfold

Pheochromocytoma. In these patients (no. 7 preoperatively and no. 8–10), small repeated injections (no. 7 and 8), infusion (no. 9), or a single injection (no. 10) of piperoxan elicited moderate decreases of blood pressure; these

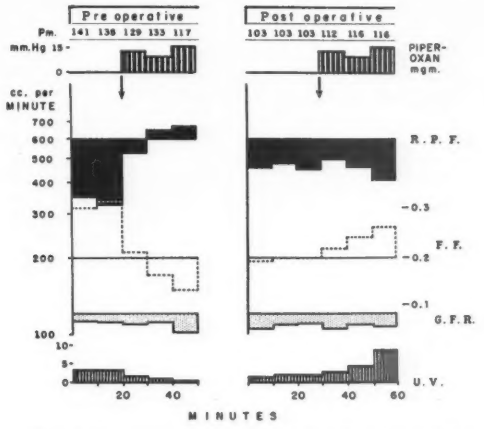

FIG. 3. Summary of preoperative and postoperative observations in patient no. 7. *Pm* indicates means of arterial pressure in each period of urine collection in mm. Hg. The piperoxan dosage in mg. is indicated next below. Renal plasma flow (*R.P.F.*) filtration fraction (*F.F.*), and glomerular filtration rate (*G.F.R.*) are plotted semilogarithmically from average normal values. Urine flow (*U.V.*) is plotted arithmetically at the bottom of the graph. The arrows indicate the beginning of the piperoxan injections. Note that *R.P.F.* reached a higher rate after piperoxan in the preoperative test than it did in the control periods postoperatively, when the hypertension had been relieved. This may represent conversion of the vasoconstrictor action of circulating epinephrine to one of vasodilatation.

decreases were associated with decreases in renal vascular resistance, which, in 2 patients (no. 7 and 8) were proportionately greater than the decreases in blood pressure (fig. 1): the postpiperoxan averages indicate 10 to 30 per cent decreases in glomerular filtration rate; urine flow decreased to about one third of the rate prevailing in the control periods (fig. 2). The postpiperoxan decreases in urine flow, like the postpiperoxan increases in urine flow in the controls, were not proportionate to the changes in filtration rate. Thus, the greatest decrease in urine flow occurred in the patient (no. 9) whose filtration rate decreased by only about 14 per cent during piperoxan infusion.

DISCUSSION

The abstracts below establish the diagnoses of functioning pheochromocytoma in patients

no. 6 to 10 and show that patients no. 7 to 10 had excess circulating adrenal medullary hormone at the time that they responded to intravenously injected piperoxan with antidiuresis.

As concerns the renal circulation, piperoxan has been shown to suppress the renal vasoconstrictor effects of epinephrine and norepinephrine in isolated perfused kidneys of dogs, more effectively in the case of epinephrine than of norepinephrine.[7] The renal vasodilatation observed in our patients with functioning pheochromocytoma during the action of piperoxan reflects this action. It may be significant that the least renal vasodilator effect was observed in the patient (no. 10) whose tumor contained norepinephrine, with only traces of epinephrine.

The experiments were not designed to test the renal mechanisms that contribute to the antidiuretic effect of piperoxan in patients with functioning pheochromocytoma, and it is likely that several mechanisms participate in the response. One is decrease in filtration rate, due to renal vasodilatation and decreased intraglomerular pressure; in general, decreases in filtration provoke proportionately larger decreases in urine flow. Another is inhibition of the renal tubular action of norepinephrine and epinephrine; current observations in this laboratory (del Greco, Masson, and Corcoran) show that in the rat small doses of these agents elicit osmotic diuresis, apparently by inhibition of proximal tubular electrolyte reabsorption, while larger doses, which cause severe renal vasoconstriction, depress urine flow by decreasing filtration rate. The third antidiuretic mechanism may be increased liberation of posthypophyseal antidiuretic hormone; this mechanism is believed to account, in part, for the antidiuretic effect of withdrawal of infusions of norepinephrine and epinephrine in patients.[1]

The pressor, renal vasoconstrictor, and, commonly, diuretic responses to injected piperoxan observed in the "control" patients are unexplained except as they may depend on known vasomotor properties of piperoxan and, since it is known to act on the brain stem and central nuclei,[8] possibly posthypophyseal inhibition.

While these mechanisms are speculative, the significant fact derived from these observations is that in patients with functioning pheochromocytoma, piperoxan has a strong antidiuretic activity, in contrast to its diuretic action in patients with hypertension due to causes other than pheochromocytoma. The antidiuretic effect of piperoxan is proportionately greater than its effect on blood pressure and on the other renal functions tested. It is clear that, under standardized conditions of hydration and diuresis, measurement of changes in urine flow may provide a simple confirmatory observation in the clinical diagnosis of functioning pheochromocytoma and may be a guard against "false positive" piperoxan tests based only on observations of arterial pressure.

Summary

Piperoxan was found to have a moderate renal vasodilatory effect and to decrease urine flow to about one third of the pretreatment rate when intravenously injected in patients with functioning pheochromocytoma. In contrast, it elicited slight renal vasoconstriction and usually increased urine flow when given to 6 patients with hypertension due to other causes and to 1 patient who had become normotensive after removal of a pheochromocytoma.

The antidiuretic effect of piperoxan in the presence of functioning pheochromocytoma probably reflects inhibition of the renal vascular and tubular actions of norepinephrine and epinephrine and, insofar as it may correspond to the antidiuresis elicited by withdrawal of infusions of epinephrine or norepinephrine, may also involve posthypophyseal antidiuretic action. The diuretic effect of piperoxan in subjects without pheochromocytoma is probably due to a similar complex response.

The antidiuretic effect of piperoxan in patients with pheochromocytoma is larger proportionately than its effect on blood pressure, so that measurement of urine flow under standardized conditions should be a simple, confirmatory sign in the diagnosis of this condition.

Acknowledgment

We are indebted to Drs. E. Perry McCullagh, Robert Schneider, Penn Skillern, and James Cook, Department of Endocrinology, Dr. Stanley O. Hoerr,

Department of General Surgery, and Dr. Eugene Poutasse, Department of Urology, for the opportunities of making observations on patients no. 5, 8, 9, and 10.

Summario in Interlingua

Esseva constatate que piperoxano ha un moderate effecto vasodilatatori renal e reduce le fluxo urinari a circa un tertio del nivello pre-tractamental quando illo es injicite intravenosemente in patientes con pheochromocytoma functionante. Del altere latere, le droga causava leve grados de vasoconstriction renal e usualmente un augmentate fluxo urinari quando illo esseva administrate a 6 patientes con hypertension debite a altere causas e a 1 patiente qui habeva redevenite normotensive post le ablation de un pheochromocytoma.

Le effecto antidiuretic de piperoxano in le presentia de pheochromocytoma functionante reflecte probabilemente un inhibition del effecto de norepinephrina e epinephrina super le activitate reno-vascular e reno-tubular. In tanto que illo corresponde al antidiurese evocate per le suppression de infusiones de epinephrina o norepinephrina, illo pote etiam involver un action antidiuretic posthypophyseal. Le effecto diuretic de piperoxano in subjectos sin pheochromocytoma es probabilemente le resultato de un responsa similemente complexe.

Le effecto antidiuretic de piperoxano in patientes con pheochromocytoma es proportionalmente plus grande que su effecto super le pression sanguinee, de maniera que le mesuration del fluxo urinari sub conditiones standardisate deberea esser un simple signo confirmatori in le diagnose de iste condition.

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Appendix

Patient no. 6 (674-592). This 61-year-old woman (patient of Dr. Robert Schneider) complained of "spells" and diabetes. Piperoxan was deeply depressor on 2 occasions, as was also phentolamine (Regitine), while histamine and dimethyl-fluorophosphate were pressor. A pheochromocytoma weighing 35 Gm. was removed from the region of the right adrenal gland and yielded 0.29 mg./Gm. of epinephrine and 0.34 mg./Gm. of norepinephrine (colorimetric assay with iodine). The arterial pressure remained elevated postoperatively, although specific tests were negative for pheochromocytoma. She was readmitted for re-exploration on the assumption that there might be a contralateral pheochromocytoma, at which time the test of renal function was done. A 5-Gm. tumor was removed from the left adrenal gland; this contained by pressor assay in the dog the equivalent of 0.1 mg./Gm. pressor urine as compared with norepinephrine and was histologically a cortical adenoma. The urine was examined by Dr. M. Goldenberg, who failed to find increased amounts of catecholamine; postoperatively, as preoperatively, piperoxan was pressor in test doses and Regitine depressor.

Patient no. 7 (673-532). This woman of 47 years was seen in August 1952 because of nervousness, sweating, palpitation, and weight loss with lower abdominal pain. The process seems to have started in 1950; in June 1951 she had been hospitalized because of "nervous collapse," consulted a psychiatrist in September of that year and, following discovery of elevated basal metabolic rate (+22), in November was treated ineffectually with propylthiouracil. Histamine was pressor and the effect was reversed with piperoxan. Dimethyl-fluorophosphate (DMPP) was pressor and Regitine depressor. Basal metabolism was measured as +50 per cent. The urine contained increased amounts of catecholamine (bioassay and iodine colorimetry) of

the order of 3 mg./24 hr. A pheochromocytoma was excised from the region of the left adrenal gland; the tumor weighed 42 Gm., and contained 0.97 mg./Gm. of epinephrine and 70 per cent (2.67 mg./Gm.) of norepinephrine. The diaphoresis and hypertension were completely relieved. The patient has continued to complain of fatigability, constipation, and abdominal and joint distress.

Patient no. 8 (680-495). This young man of 22 years was admitted to the hospital in November 1952 with the diagnosis of pheochromocytoma made on the basis of sudden onset of hypertension, a depressor response to piperoxan, and an elevated basal metabolic rate (+42). His attacks occurred about twice weekly over 6 months and consisted of headache, violent heart action, anxiety, tremor, and blurred vision with sweating. Prerenal air insufflation demonstrated what seemed to be bilateral tumors in the region of the adrenal glands. These were excised; the tumor from the left side weighed 22 Gm. and of its total catecholamine (colorimetric assay) of 1.7 mg./Gm., 89 per cent was norepinephrine; the tumor from the right weighed 20 Gm. and had a catecholamine content of 3.5 mg./Gm., of which 50 per cent was norepinephrine. The histology was such that malignant disease was suspected, although the tumors had not invaded their capsules. Since operation, the patient has been asymptomatic and the response to piperoxan became weakly pressor, although moderate hypertension has persisted.

Patient no. 9 (711-983). This woman of 57 years complained principally of excessive perspiration of 1 year's duration; hypertension had been present for 5 years and hypermetabolism (+50 to +70) demonstrated 2 years before. A feeling of warmth with sweating and palpitation had distressed her for about 1 year. Regitine and piperoxan yielded depressor responses and histamine was pressor. A laminagram showed a possible mass in the region of the left adrenal gland. At operation this lay medial and anterior to the upper pole of the kidney. The tumor invaded the adrenal vein and was presumed to be malignant. It weighed 70 Gm. and an extract of it indicated a pressor activity equivalent to 14 mg./Gm. of pressor amine in terms of norepinephrine. Her complaints and her hypertension were relieved by operation, after which also she began rapidly to gain weight. Preoperatively, the urine contained increased amounts of catecholamine (Dr. Marcel Goldenberg).

Patient no. 10 (751-541). This 17-year-old girl (a patient of Dr. Wm. Leonard, Jr.) was referred to the Cleveland Clinic (Drs. Stanley O. Hoerr and Eugene F. Poutasse) with the diagnosis of pheochromocytoma, based on frequent, disabling episodes of pounding headache, profuse perspiration, palpitation, and nervousness, lasting about 10 minutes and often precipitated by emotional tension with hypertension (admission, 210/130) of about 1 year's duration. The blood sugar tolerance was impaired; the basal metabolic rate was increased (+31 per cent). Regitine (5 mg. i.v.) decreased blood pressure from 230/150 by 80/60 mm. Hg. Bioassay (Dr. R. Schneckloth) indicated the presence in urine of the pressor equivalent of 1 μg. norepinephrine/ml. At operation the tumor was found at the bifurcation of the aorta, adherent to the vena cava, apparently by extension through the capsule. Peaks of pressure during operation were controlled with Regitine, and pressure was maintained postoperatively at about 120/80 by infusion of norepinephrine. Regitine tests were repeated 1 week postoperatively, with initial pressures of 140/110 and 160/110 with negative results. Provocative histamine tests were done at 1 week and at 3 months with initial pressures respectively of 160/110 and 126/80, also with negative results. Symptoms have completely disappeared. The tumor weighed 54 Gm., was histologically well differentiated, but was diagnosed as malignant because of its invasiveness. Dr. Marcel Goldenberg informed Dr. E. Perry McCullagh that it contained traces of epinephrine and 1.87 mg. of norepinephrine/Gm. Dr. Goldenberg's estimate of the urinary excretion of norepinephrine corresponded to that made by Dr. Schneckloth.

West, G. B., and Taylor, N. R. W.: Studies in Phaeochromocytoma: III. The Excretion of Noradrenaline in the Urine of Cases of Hypertension and Its Value in the Diagnosis of Phaeochromocytoma. Glasgow M. J. **36:** 123 (April), 1955.

In 200 cases of hypertension, the noradrenaline excretion in the urine was found to be below 80 μg./24 hours. In 3 cases of pheochromocytoma this excretion ranged between 225 and 750 μg./24 hours, but fell to normal levels following operation. It is considered that the estimation of urinary pressor amines offers the best available special method of diagnosis of pheochromocytoma.

BERNSTEIN

Rauwolfia serpentina in the Treatment of Angina Pectoris

By Bernard I. Lewis, M.D., F.R.C.P. (C), Robert I. Lubin, M.D., L. E. January, M.D., and John B. Wild, M.D., M.R.C.P. (Lond.)

Fifteen subjects with coronary artery disease and angina pectoris were given alternate courses of the alseroxylon fraction of *Rauwolfia serpentina* and placebo. Fourteen improved on the drug as determined by independent clinical evaluations and the "Daily Report Card" data. Seven developed normal electrocardiograms, 2-step tests or ballistocardiograms, that previously had been abnormal. Alseroxylon appeared to induce an unusually prolonged therapeutic effect that was revealed only by an individual "sequential" analysis of each course of drug and placebo. The nature of the underlying mechanism is not clear. Serious hypotensive responses and acute depressive reactions are infrequent at the dosage levels used, but do occur.

In a recent report of the therapeutic spectrum of *Rauwolfia serpentina*,* we included some preliminary observations on its use in the anginal syndrome.[1] This paper is a more detailed evaluation of the therapeutic responses of 15 ambulatory subjects with coronary artery disease and angina pectoris whom we have now studied for an average period of 42 weeks each.

Case Material

There were 13 men and 2 women in the study group (table 1). Their mean age was 59 years. As a group, they had experienced frequent, severe anginal attacks for an average period of 26 months. Four subjects had historical and electrocardiographic evidence of previous myocardial infarction that had occurred at a mean time of 27 months before admission. Ten subjects presented abnormal electrocardiograms, 9 of whom also had abnormal ballistocardiograms.[2] Of the 5 with normal admission tracings, there were 4 with positive 2-step exercise tests[3] and 3 with abnormal ballistocardiograms. The fifth subject, who had a negative 2-step test, showed ballistocardiographic abnormalities. Seven subjects gave a history of arterial hypertension and had entrance blood pressures in excess of 150/100 mm. Hg. All subjects had been doing poorly or had ceased to improve on conventional therapy. During this study they received no medication other than nitroglycerin as needed and either alseroxylon or placebo.

Study Plan

In accordance with the double blind technic, one physician examined the subject at each visit and recorded an independent clinical evaluation. A second physician then saw the patient, collected the "Daily Report Cards," which we will describe shortly, and prescribed by code number either the active drug or an identical placebo tablet. These agents were given in alternate courses of 6 or more weeks. In all but 2 cases, the placebo was prescribed first to provide an initial baseline period and to assess any psychologic response.

Various laboratory procedures were performed on admission and at each return visit. These included 12-lead electrocardiograms, 2-step exercise tests, velocity-type ballistocardiograms, and teleroentgenograms for cardiac size and contour. These were interpreted by physicians who had no additional contact with the subjects.

The "Daily Report Card" is a special chart for subjective evaluations and is a modification of the type devised by Greiner and his associates.[4] This card makes but 2 simple demands (fig. 1). First, the subject must grade his angina each day in comparison with his average pretreatment level, by marking an "X" in the appropriate section and second,

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* Riker Laboratories, Inc., supplied the alseroxylon (Rauwiloid) used in this study and aided in its support.

TABLE 1.—*Case Material*

Number of subjects:	15 (13 men, 2 women)
Age:	
mean	59 years
range	35–68 years
Duration of angina (mean)	26 months
Severity of angina:	
severe	5 subjects
moderately severe	10 subjects
Prior myocardial infarction	4 subjects
Time of infarction (before admission):	
mean	27 months
range	5–46 months
Admission electrocardiogram:	
abnormal	10 subjects
normal	5 subjects
Positive "2-step" test	4 subjects
Abnormal ballistocardiogram	12 subjects
Duration of observation (mean)	42 weeks
Incidence of hypertension (B.P. 150/100 mm. Hg or more)	7 subjects

he must record his nitroglycerin intake and actual number of anginal attacks for each 24-hour period. Each card thus provides a daily account of the frequency and severity of the angina over a 31-day interval.

These "Report Cards" have the virtues of simplicity and tangibility. They supply a large volume of data for statistical analysis. In contrast to most subjective evaluation technics, the "Daily Report Card" tends to prevent errors from memory lapses, from undue emphasis on temporary fluctuations in symptoms, and from misleading statements made to the doctor.

RESULTS

Table 2 is an analysis of all the combined "Report Cards" for the entire group. Here, the results of all courses on drug are compared with those of all the placebo periods. The

"DAILY REPORT CARD" FOR HEART PAIN

BRING THIS REPORT CARD WITH YOU EACH VISIT

NAME JOSEPH N. DATE TREATMENT STARTED 3/15/54

HOW MUCH HEART PAIN DID YOU HAVE EACH DAY?	DAY OF WEEK																												
	MON	TUES	WED	THUR	FRI	SAT	SUN	MON	TUES	WED	THUR	FRI	SAT	SUN	MON	TUES	WED	THUR	FRI	SAT	SUN	MON	TUES	WED	THUR	FRI	SAT	SUN	MON	TUES	WED
SAME HEART PAIN AS USUAL		X								X																				
LESS HEART PAIN THAN USUAL GOOD DAY	X		X	X				X	X			X		X		X				X	X	X	X			X	X	X		
MORE HEART PAIN THAN USUAL BAD DAY					X	X					X		X											X						
NO HEART PAIN AT ALL							X								X		X	X	X						X					
NUMBER ATTACKS OF HEART PAIN PER DAY	1	2	1	1	3	3	0	1	1	2	3	1	4	1	0	2	0	0	0	1	2	1	1	4	0	2	2	1		
NUMBER NITROGLYCERINE TABLETS PER DAY	1	2	1	1	3	3	0	1	1	2	3	1	4	1	0	2	0	0	0	1	2	1	1	4	0	2	2	1		

BEFORE GOING TO BED EACH NIGHT, WRITE A MARK (X) IN THE SPACE THAT DESCRIBES YOUR HEART PAIN FOR THE ENTIRE DAY AND WRITE IN THE NUMBER OF HEART ATTACKS AND NITROGLYCERINE TABLETS TAKEN THE ENTIRE DAY.

FIG. 1. Example of Daily Report Card used for subjective evaluations

data on frequency of angina and nitroglycerin intake correlated very closely and have been omitted. On the basis of this combined analysis the total group responses to these 2 agents appear strikingly similar. The minor differences here are not statistically significant.

Table 3 is an individual analysis of the "Report Card" data of each subject (again based on a comparison of the combined drug courses and the pooled placebo periods). The purpose here was to detect any subjects who might have improved on one or the other agent but whose results were obscured by others who did poorly. On the left half of the table, it will be seen that, whereas 3 subjects did better on drug, 2 seemed to improve on placebo, and the majority responded similarly to both agents. From this individual analysis there again appears to be no evidence of any significant therapeutic superiority for alseroxylon.

We did not expect, therefore, to have the independent clinical evaluations indicate unequivocal improvement in all but 1 subject, but such was the case. The basis for these apparently divergent results became clear on re-examination of the "Report Card" data. When we analyzed separately each successive observation period of each subject, we noted a curious sequence of therapeutic events. In essence, after the initial baseline period on placebo, 11 of the 15 subjects had distinctly improved when given alseroxylon. Then, and this was the unexpected finding, these subjects maintained their improvement when placebo was substituted and thereafter exhibited a stepwise pattern of progressive improvement during the subsequent courses of drug and placebo.

The bar graphs in figure 2 illustrate this therapeutic pattern in 2 representative subjects. The light bars represent the percentage of days free of angina, the upper shaded areas are the "Good Days" (i.e., less angina than usual) and the lower black zones are the "Bad Days" (i.e., when the angina was unusually severe). The "Unchanged Days" (i.e., angina same as usual) contribute no differential information and have been omitted from these graphs. For this reason the individual bars usually total less than 100 per cent. The progressive improvement on alseroxylon is now quite apparent, as is its curious persistence during the following placebo periods. This phenomenon was masked in our initial analyses because we had combined the data of all alseroxylon courses and compared them with the pooled placebo results.

A final evaluation of the "Report Card" data is based on these individual "sequential" analyses (table 4). We now find that 14 subjects had improved with treatment. Three of the 14 regressed during placebo administration

TABLE 2.—*Comparison of Rauwiloid and Placebo by "Daily Report Card" Method, Analysis of Group Data*

Agent	No. of days reported	Percentage of days in which angina was reported as:			
		Unchanged (same)*	Increased (bad day)	Reduced (good day)	Absent (no pain)
Rauwiloid	2167	18	11	35	36
Placebo	2232	16	9	31	44

* Terms in parentheses used on "Daily Report Cards."

TABLE 3.—*Comparison of Rauwiloid and Placebo by "Daily Report Card" Method, Analysis of Individual Data*

Group	No. of patients	No. of days reported		Percentage of days in which angina was reported as:					
				Increased (bad day)*		Reduced (good day)		Absent (no pain)	
		R	Pl	R	Pl	R	Pl	R	Pl
1. Rauwiloid "Superior"	3	524	477	9	14	40	30	40	33
2. Placebo "Superior"	2	261	218	21	5	33	38	10	35
3. Rauwiloid and placebo equal	10	1382	1537	10	8	34	30	39	49

* Terms in parentheses used on "Daily Report Card."

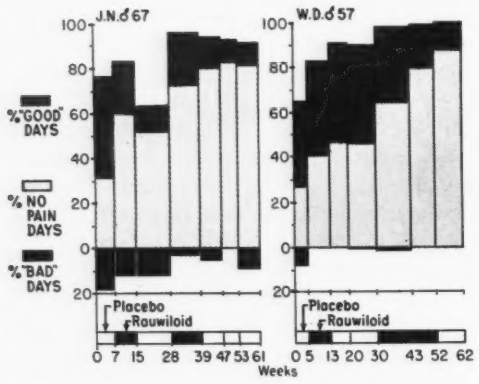

FIG. 2. Bar graphs demonstrating the progressive and sustained therapeutic response pattern after Rauwiloid.

TABLE 4.—*Evaluation on Basis of Sequential Use of Rauwiloid and Placebo*

Therapeutic response pattern	No. of subjects
Improved with Rauwiloid—worse with placebo	3
Improved with Rauwiloid—maintained with placebo	11
No benefit from either Rauwiloid or placebo	0
Worse with Rauwiloid	1
	15

TABLE 5.—*Comparison of Therapeutic Results as Determined by Clinical and "Daily Report Card" Methods*

Method of evaluation	Degree of improvement			Unchanged	Worse
	Marked	Moderate	Mild		
Clinical	9	3	2	1	0
"Daily Report Card"	3	6	5	0	1

but, as we have seen, the other 11 sustained their improvement on this agent. Only 1 subject experienced more angina with alseroxylon, and a possible factor here was the marked fall in blood pressure, presumably induced by the drug.

Table 5 compares the clinical and "Report Card" estimates of the degree to which each subject improved. These evaluations are quantitatively quite dissimilar. Though we can not be sure which is the more accurate we suspect that the clinical opinions may have been unduly influenced by the general enthusiasm and optimism the subjects exhibited.

LABORATORY RESULTS

Seven subjects demonstrated noteworthy improvement in their serial laboratory tests during the course of this study. Four developed normal electrocardiograms but on occasion during the intervening placebo periods, 2 of these again became abnormal. In 5 cases positive 2-step tests were converted to negative with only 1 reverting on placebo. One subject achieved a normal ballistocardiogram while receiving alseroxylon and another exhibited marked though incomplete improvement; when placebo was administered the tracings of both regressed. These laboratory changes tended to follow an alternating pattern, becoming normal with alseroxylon, reverting with placebo, and becoming normal again with the active drug. The x-ray studies failed to reveal any notable changes in heart size or contour.

We do not mean to imply that these laboratory changes were the direct results of therapy. There is insufficient evidence to support such a conclusion. We are well aware of the role of time and spontaneous change in patients with coronary artery disease and wish to note only that these laboratory findings did occur and were coincidental with the administration of alseroxylon.

Figure 3 presents the pretreatment and post-treatment 2-step tests of a subject whose tracings became normal on drug and then reverted on 3 occasions with placebo.

There was little correlation between these laboratory fluctuations and clinical status. After initial improvement, these subjects continued to feel well, even when their tracings deteriorated on administration of placebo.

Alseroxylon reduced the arterial blood pressure and, more consistently, slowed the heart rate of all 15 subjects. The 7 subjects with improved tracings demonstrated an average decrease of 18 mm. Hg in mean arterial blood pressure and 13 beats/min. in heart rate.

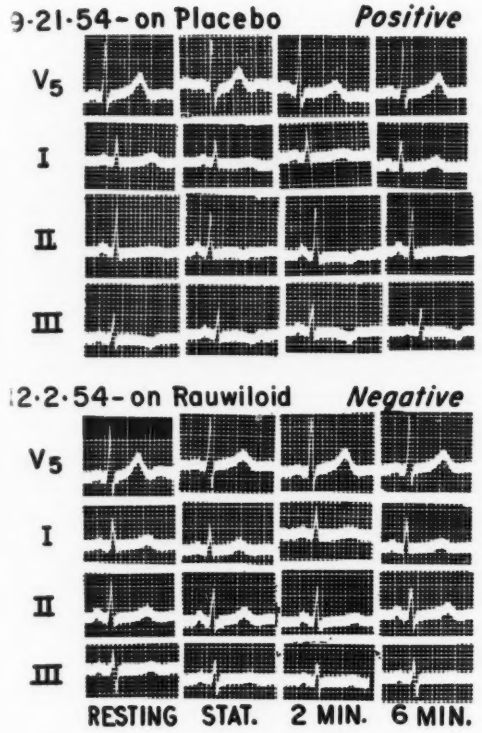

FIG. 3. Example of conversion of positive 2-step test to negative after Rauwiloid therapy.

For the 8 without laboratory changes, the results were almost identical—mean reductions of 16 mm. Hg and 12 beats/min., respectively. There was a similar lack of correlation between these changes in pressure and rate and the relative degree of improvement in anginal status. The possibility is not excluded, however, that these reductions were importantly related to the therapeutic results.

DISCUSSION

In certain respects, these results raise more questions than they answer. It is clear that, with a single exception, all subjects improved on treatment. None developed myocardial infarction or cardiac decompensation during the study. Their characteristic course was one of progressive reduction in frequency and severity of angina and steady increase in effort tolerance.

It does not seem likely that 14 of the 15 subjects spontaneously improved to this degree without relation to therapy. Nor do we believe that iatrogenic factors played a significant role here. The study plan that divided the subject's care among several physicians tended to prevent any close doctor-patient relationships. All subjects were aware of the experimental nature of the program. All physicians tried to maintain impersonal attitudes and deliberately "treated the disease, not the patient." These factors militate against any potent psychotherapeutic role by the members of the research team.

The nature of the prolonged therapeutic effect after alseroxylon is a puzzling feature. It persists well beyond the range of direct pharmacologic action that we had defined in our earlier studies.[1] Undoubtedly alseroxylon's so-called tranquilizing effect may have helped some subjects who were unduly apprehensive about their heart disease, with benefit to their anginal state. In addition, however, we believe it likely that a more efficient and apparently relatively self-sustaining physiologic balance between coronary supply and myocardial demand was pharmacologically established. Whether this effect was mediated directly through the drug's cardiovascular action or indirectly through the central nervous system is not clear. The recent studies[5, 6] by Brodie and his group on the relationship of serotonin and rauwolfia derivatives may shed further light on some of the basic mechanisms involved.

Despite the satisfying results achieved by these subjects, a note of therapeutic caution should be introduced. Rauwolfia preparations must not be employed indiscriminately. Untoward reactions do occur. Some individuals may experience a fall in arterial blood pressure of sufficient magnitude to increase dangerously their preexisting coronary insufficiency. This may well have been the case in our subject whose angina worsened on the drug. A similar sequence of events has been reported elsewhere.[7] Although this has occurred infrequently in our experience, we have nonetheless proceeded very cautiously with hypertensive and arteriosclerotic patients. We have not

observed such reactions in normotensive patients.[1]

Psychologic factors provide another potential problem. Many patients become emotionally disturbed on learning of their coronary artery disease. For those with states of anxiety and tension we have found alseroxylon most effective. Contrariwise, subjects with depressive features, with or without vascular disease, do not do well. A deepening of the depression tends to occur, and suicide becomes a real threat. We believe it mandatory, therefore, to evaluate the psychologic climate before prescribing rauwolfia preparations and to avoid their use when a significant depressive component is present.[1]

We have found that these and other undesirable effects are more likely to develop as the dosage level increases. We have tried various schedules and believe that 4 mg./day of alseroxylon will achieve a maximal therapeutic response about as rapidly as larger amounts. The minor side-effects at this level have been well tolerated by our patients and potentially serious reactions have been rare.

The very nature of the anginal syndrome and the spontaneous variations in its course have always made therapeutic trials most difficult to undertake and assess. Our evaluating technics have not overcome these inherent difficulties but we believe this combination of objective, subjective, and laboratory methods has minimized them. Certainly this multiple approach was, for us, superior to any single method of assessment.

Summary

Alseroxylon appeared to be an effective adjunct to the management of the subjects with angina pectoris in this study, although its mode of action remains unclear.

Summario in Interlingua

Dece-cinque subjectos con morbo de arteria coronari e angina de pectore recipeva in alternation cursos del fraction alseroxylona ab Rauwolfia serpentina e de un medication fictitie. Dece-quatro se meliorava sub le effectos del droga secundo independente evalutationes clinic e le datos del "Carta de Reportage Diurne." In septe casos, previemente anormal electrocardiogrammas, tests a duo passos, e ballistocardiogrammas deveniva normal. Alseroxylona pareva inducer un inusualmente prolongate effecto therapeutic que esseva revelate solmente per individualisate analyses "sequential" de omne curso del droga e del medication fictitie. Le natura del mechanismo involvite in le action del droga non es clar. Serie responsas hypotensive e acute reactiones depressive es infrequente al nivellos de dosage usate, sed illos non es absente.

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Left Axis Deviation

An Electrocardiographic-Pathologic Correlation Study

By ROBERT P. GRANT, M.D.

Our understanding of the meaning of the electrocardiogram is greatly furthered by careful comparison of cardiac hypertrophy and cardiac damage observed post mortem with electrocardiograms taken during the last weeks of life. An electrocardiographic-pathologic correlation of 672 cases is reported in which the roles of left ventricular hypertrophy, myocardial infarction, and other factors in the production of left axis deviation are examined. A heretofore unrecognized QRS-complex syndrome of infarction is described in which the QRS forces are diagnostically abnormal but no "Q waves" are seen in the conventional leads. The roles of hypertrophy, variations in body build, chronic pulmonary disease, and various types of "parietal block" in the production of left axis deviation are studied.

LEFT axis deviation (*LAD*) is one of the commonest abnormalities encountered in clinical electrocardiography. When unassociated with other electrocardiographic abnormalities, it is usually considered of little clinical significance and is attributed to a leftward anatomic position of the heart, to incomplete left bundle-branch block, or perhaps to left ventricular hypertrophy. Recent observations, however, suggest that none of these is a common cause of *LAD* and that other factors, some of clinical importance, are more frequently the cause.

In the first place, detailed anatomic-electrocardiographic studies have shown that cases with marked *LAD* do not necessarily have a more leftward direction of the anatomic long axis of the left ventricle than do cases with more normally directed electric axes. Indeed, there proved to be very little variation in the position of the left ventricle in the chest in a wide variety of cardiac conditions.[1] Furthermore, evidence has been presented that incomplete left bundle-branch block as ordinarily defined is an exceedingly uncommon electrocardiographic syndrome, and this evidence will be discussed further. Finally, it has been shown that myocardial infarction frequently causes an alteration in the direction of the last electric forces to be generated during the QRS interval. On comparing preinfarction and postinfarction tracings in a large number of subjects it was found that nearly half show this alteration in terminal QRS vector without significant prolongation of the QRS interval, and that in a large number of these cases the terminal QRS alteration produced marked *LAD*.[2] In order further to evaluate the relationship of infarction, hypertrophy, and other myocardial abnormalities to the incidence of *LAD* a clinico-pathologic-electrocardiographic correlative study was undertaken.

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METHODS AND MATERIAL

Six hundred seventy-two consecutive cases were collected in which complete autopsies had been performed and electrocardiograms had been recorded within 5 weeks of death.* From the electrocardiographic point of view, the tracings were examined for the incidence of (1) deformity of the initial QRS electric forces diagnostic of myocardial infarction by current generally accepted criteria outlined below; (2) significant left axis deviation (i.e., the mean QRS vector directed more leftward than −15 degrees on the triaxial reference figure); (3) left ventricular "strain" (i.e., mean spatial ST and T vectors relatively parallel with each other and both more than 160 degrees from the direction of the mean spatial QRS vector, whether with or without *LAD*); and (4) the amplitude of the QRS

* The author wishes to thank the members of the heart stations and Departments of Pathology of Georgetown University Hospital, George Washington University Hospital, Mount Alto Veterans Hospital of Washington, D.C., and the Clinical Center of the National Institutes of Health for their generosity and cooperation in this study.

complexes in the limb leads and precordial leads, to be correlated with the heart weight and body build for a given mean QRS axis direction. Cases with QRS intervals of .12 sec. or more were not included in the study. In all cases the conventional 12-lead electrocardiogram had been recorded with V leads.

From the point of view of the autopsy correlations, the cases were obtained from hospitals connected with medical schools where, in view of the teaching activity, the postmortem examinations might be presumed to be more than usually comprehensive and detailed. However, since in nearly all cases the autopsies had been completed before this study was begun, and since no special studies in cardiac pathology were being conducted in these hospitals, it must be assumed that the postmortem examination of the hearts was no more than "routine" in its meticulousness in most cases. However, the type of information sought from the postmortem examination for this study was simple and not likely to have been overlooked or measured incorrectly. The autopsy protocols were studied for (1) the presence of myocardial infarction, seen grossly and confirmed histologically, without regard to its size, age, location, or the likelihood that more than 1 infarct might have been present; (2) the amount of fibrosis on histologic examination; and (3) the incidence of left ventricular hypertrophy. Measurements of wall thickness and descriptions of the diameter of myocardial fibers were found to be supportive but not in themselves unequivocal evidence of left ventricular hypertrophy. Therefore, the gross weight of the heart was used to identify these cases. It is recognized that this is an extremely crude index of left ventricular size, especially if the increase in weight is slight, and that cases with large mural thrombi or excessive epicardial fat might be erroneously included among cases of left ventricular hypertrophy by this method. However, for the particular purposes of this study it was more important that no case of *marked* left ventricular hypertrophy be overlooked than that all cases of even slight hypertrophy be included. Therefore, hearts weighing over 500 Gm. were considered to be instances of left ventricular hypertrophy if the measured thickness of the left ventricular wall was increased, and if no other cause of the increased weight had been described. This is a considerably greater heart weight than is usually used to identify hypertrophy but has the virtue of more clearly separating cases of marked hypertrophy from those that might be normal. In all cases with left ventricular hypertrophy an etiology was sought in the clinical record on the autopsy protocol to confirm the diagnosis; in all but a few instances such factors could be identified.

Of course the QRS changes ascribed to left ventricular hypertrophy reflect only an increase in ventricular size, whether due to hypertrophy or dilatation or both.[3] Unfortunately, the technic used in most Departments of Pathology for dissecting the heart does not permit objective measurement of the degree of left ventricular dilatation in a given heart, and this was true of the cases in this study. It was necessary to assume that the cases with marked dilatation of the left ventricle had also an increase in total heart weight, which is probably true in most cases.

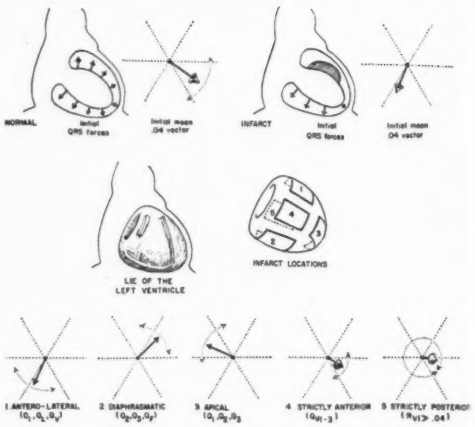

FIG. 1. Mechanism of the deformity of initial QRS forces in myocardial infarction, with QRS deformity criteria for 5 general electric locations of infarction.

The major cause of death was noted in each case. The presence of other intrathoracic abnormalities, especially pulmonary emphysema, was noted, whether or not it had been a major cause of death. The body height and weight at the time of death were recorded for each case in the autopsy protocol. No cases under 30 years of age were included in the study. By the fortunes of case incidence there were no instances of congenital heart disease, cardiac amyloidosis, cardiac scleroderma, or other unusual types of heart disease in the series. Four cases, all with increased heart weight, were judged by the pathologist to be cases of "myocarditis." Two of these had QRS changes indistinguishable from those of infarction.

A word should be said about the QRS criteria used for the electrocardiographic diagnosis of infarction. As shown schematically in figure 1, the left ventricle is a conical structure that normally lies somewhat horizontally in the cardiac silhouette. From a topographic point of view it can be considered to consist of 5 general regions, as shown, and an infarct may involve any of these regions or the zones between them. Infarction produces QRS complex deformity by causing the electric forces during the first .04 sec. of the QRS interval to be altered in direction. As a result, when the mean vector for the first .04 sec. of the QRS interval is plotted on the

iaxial reference figure, it points away from the gion of the heart involved electrically by the infarct, as shown. It is the particular direction of these initial forces of the QRS interval that accounts for the abnormal "Q waves" on certain of the leads in such cases. Thus the "Q wave" patterns for different electric locations of infarction can be systematized by drawing the mean vector for the first .04 sec. of the QRS interval for each location. This is shown at the bottom of figure 1 for each of the 5 topographic locations of the left ventricle. These 5 directions of initial .04 vectors embody the QRS complex criteria used in this study.

The electric locations may or may not coincide with the actual anatomic location of the infarct. In the present study, there appeared to be at best a general similarity between the electric location of infarction and its anatomic locations as described at autopsy; however, frequently there was no agreement whatever. This should not be surprising, since the electric effects and the histologic effects are quite different manifestations of infarction and there is no reason why they should necessarily coincide in location. In the discussion that follows the use of anatomic terms to identify infarction (e.g., "anterolateral infarction") is meant to indicate the type of QRS complex deformity produced by the infarct and not necessarily the actual anatomic location of the infarct. No attempt is made in this study to test present-day QRS criteria for the diagnosis of infarction against the findings at pathologic examination except as they bear on the problem of left axis deviation. The relative incidences of electrocardiographic and autopsy findings used in this study are shown in table 1.

TABLE 1.—*Electrocardiographic and Autopsy Findings in 672 Consecutive Cases*

Total cases.....672				
1. Myocardial Infarction.....160	Antero-lateral...47			
	Others.....113			
Left Ventricular Hypertrophy (no myo. infarct)...73	Left axis.....35			
	Normal axis.....35			
	Vertical axis.....3			
Controls (under 500 Gm., no myo. infarct).....439	Left axis.....42			
	Others.....397			
	Myo. Inf.....54	Anterolat.....34		
		Others.....20		
2. Left Axis Deviation.....131	No Infarct.....77	Ht. wt. over 500 Gm.....35		
		Ht. wt. 400-500 Gm.....19		
		Ht. wt. under 400 Gm.....23		
3. R′ deflections at V-1 or V-2 or both.....46	Myo. Infarct....12		$R_1S_2S_3$.....8	
			$S_1S_2S_3$.....4	
			$S_1R_2R_3$.....0	
	LVH with *LAD* 6		$R_1S_2S_3$.....3	
			$S_1S_2S_3$.....3	
			$S_1R_2R_3$.....0	
	LVH without *LAD*.....0			
	Normal ht. wt. with *LAD*.....7		$R_1S_2S_3$.....4	
			$S_1S_2S_3$.....2	
			$S_1R_2R_3$.....1	
	Normal ht. wt. without *LAD* 21		$R_1S_2S_3$.....0	
			$S_1S_2S_3$.....8	
			$S_1R_2R_3$.....13	

Left Ventricular Hypertrophy As a Cause of Left Axis Deviation

It is generally believed that left ventricular hypertrophy (*LVH*) is a cause of left axis deviation (*LAD*); indeed, *LAD* has often been considered an important if not essential criterion for the electrocardiographic diagnosis of *LVH*.[4, 5] Therefore, the relationship between heart weight and the incidence of *LAD* was studied. When cases with proved myocardial infarction were excluded, there were 77 cases with *LAD*. Only 35 of these (less than half) had heart weights of 500 Gm. or more; 19 had hearts weighing 400 to 500 Gm., and 23 had hearts weighing less than 400 Gm. Thus *LAD* is by no means diagnostic of *LVH*. Nor is the development of *LAD* dependent upon the severity of the *LVH*; among the 9 cases with hearts over 900 Gm. due to *LVH*, 6 had normally directed electric axes and only 3 had *LAD*.

This poor correlation of *LAD* and *LVH* was somewhat unexpected, so that the question was raised whether variations in body build might have influenced the results, a lean subject having a more vertical axis and a stocky subject a more leftward axis for a given heart weight. The body height and weight for each subject at the time of death had been entered in the autopsy protocol, and therefore this possibility could be studied. In figure 2 all cases of *LAD* and left ventricular "strain" and, in addition, all cases with hearts weighing over 500 Gm. (excluding those with infarctions at autopsy) are plotted in terms of heart weight and body build; then, for each type of body build, the cases are divided into those with normally directed electric axes, and those with *LAD*. For a given heart weight, whether or not it was greater than normal, the incidence of *LAD* was no greater among the stocky subjects (those overweight for the

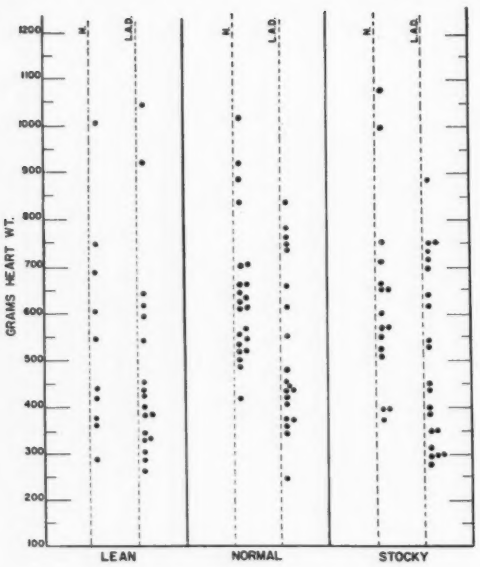

FIG. 2. Effect of body build and heart weight on the direction of the mean QRS axis. The cases are distributed on the abscissa according to normal or left axis deviation for 3 types of body build.

stated body height) than among lean subjects (those underweight for the stated height). In fact, there were certain lean subjects with normal or less than normal heart weights who had marked *LAD* while certain stocky subjects with tremendous *LVH* had normally directed electric axes. This does not mean that body build is without influence on the direction of the electric axis, but only that this influence is slight in most instances. In a previous study, it was shown that there is rarely more than a 20-degree variation in the direction of the anatomic long axis of the left ventricle in either the normal subject or the subject with marked *RVH* or *LVH* regardless of body build.[1] In conclusion, while a stocky body build might cause *LAD* to become more leftward or a lean body build might cause a normal axis to become more vertical, it is apparent that neither variations in body build nor variations in the anatomic position of the heart can alone be responsible for *LAD*.

It must not be overlooked that, although less than half of the cases of *LVH* had *LAD*, nevertheless the incidence of *LAD* is higher among cases of *LVH* than it is among patients with normal heart weights, for less than a tenth of the 439 cases with neither *LVH* nor infarction showed *LAD*. Thus, although *LVH* does not itself cause *LAD*, there is some aspect of the hypertrophy mechanism that in about half of the cases brings in its train *LAD*. Perhaps the myocardial fibrosis that so commonly accompanies marked *LVH* produces an alteration in the more peripheral parts of the left ventricular conduction network analogous to what has been called "parietal block."[6, 7]

While variations in body build do not greatly influence the direction of the mean QRS axis, they do influence the amplitude of QRS complexes in the various leads. This relation has been largely overlooked in studies concerned with establishing QRS criteria for the diagnosis of *LVH*.[8] In the present series of cases, these criteria identified over 90 per cent of cases of marked *LVH* when the body build was normal. However, in subjects either markedly overweight or underweight for their height, the criteria were totally unreliable. For example, there were 3 subjects with heart weights over 700 Gm. due to *LVH* with QRS complexes not more than 20 mm. in amplitude in the precordial leads, which is within the normal range. All 3 subjects weighed over 190 pounds and none was taller than 5 feet 6 inches. On the other hand, there were 7 cases with hearts weighing less than 450 Gm. who had QRS complex amplitudes of more than 45 mm. in 1 or more precordial leads, which are amplitudes ordinarily considered diagnostic of *LVH*. All 7 subjects weighed less than 115 pounds and their average height was 5 feet 6 inches. Thus, obesity may obscure the QRS changes of *LVH*, and leanness may account for unusually large QRS complexes when the heart is normal in weight.

There is another clinical syndrome in which the amplitude of the precordial QRS complex is greatly increased and resembles that of *LVH* but in which the left ventricle is normal in weight. This is the syndrome of mitral insufficiency with giant left atrium. In figure 3 is shown the electrocardiogram of such a patient; the very large QRS complexes and

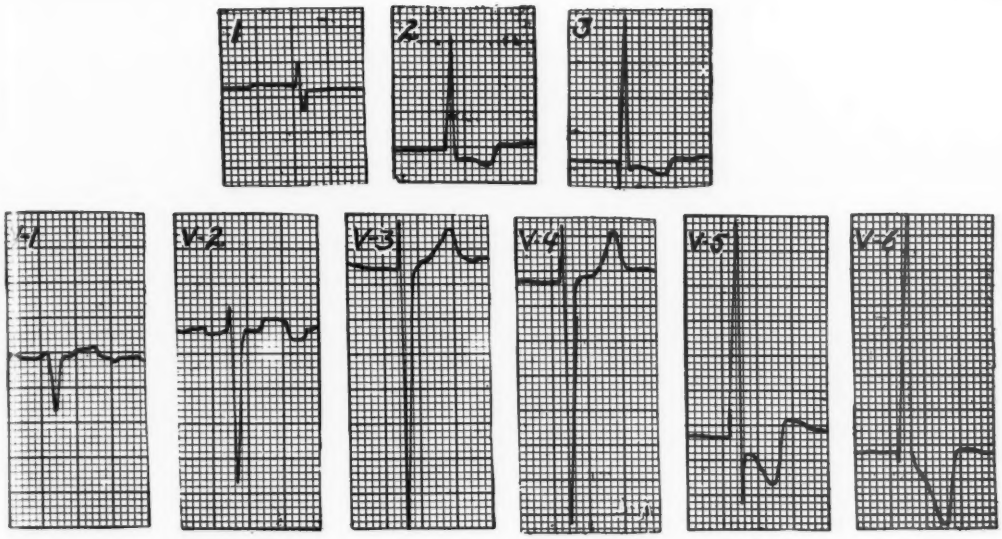

FIG. 3. Standard limb leads and precordial leads in a patient with mitral insufficiency and giant left atrium who had a normal left ventricular weight at autopsy. The QRS amplitude and ST-T inversions in certain of the precordial leads resemble those of left ventricular hypertrophy.

abnormal ST-T segments in the left precordial leads are identical with what is seen in severe *LVH*. However, the heart in this case was carefully dissected at autopsy and the left ventricle was found to be low normal in weight and not dilated. Atrophy of the posterior wall of the left ventricle, which is commonly seen in this syndrome, accounted for the reduced weight. The details of this case, including photographs of the left ventricle, have been published elsewhere.[9] The increased amplitude of the QRS complexes was due to the fact that the greatly enlarged left atrium had shifted the ventricular part of the heart much closer to the left anterior chest wall. It will be noted that the mean QRS axis is vertical in this case, as it is in most cases of rheumatic mitral regurgitation with enlarged left atrium; this position reflects right ventricular dominance and is further evidence against significant left ventricular hypertrophy or dilatation. Although it is commonly thought that uncomplicated rheumatic mitral regurgitation is associated with *LVH*, there have been no careful autopsy studies to support this belief.

Infarction and Left Axis Deviation

It is well known that myocardial infarction alters the direction of the electric forces generated during the first .04 sec. of the QRS interval. This is the deformity that accounts for the "Q waves" characteristic of infarction. Recently, it has been shown that infarction may also alter the directions of the electric forces generated during the last part of the QRS interval with little or no prolongation of the QRS interval. In about one half of the cases with QRS alterations of anterolateral infarction the terminal QRS forces are caused to point leftward and superiorly, producing *LAD*, while in an equal percentage of cases of diaphragmatic infarction they are caused to point rightward and inferiorly, often producing right axis deviation.[2]

The simplest explanation of these terminal QRS abnormalities attributes them to perinfarction block. In this explanation it is presumed that the normal radial spread of excitation from endocardium to epicardium is blocked at the region of the infarct, either because of the size of the infarct or, more likely, because certain critical regions of the

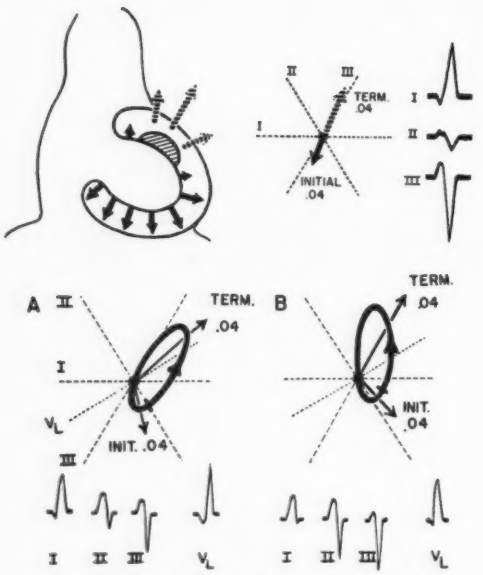

FIG. 4. Upper figures: schema of the mechanism of initial and terminal QRS vector deformity in anterolateral peri-infarction block. *A*. The typical QRS loop in anterolateral peri-infarction block with the QRS complexes; such a loop would write on the standard limb leads and lead aV_L. *B*. The loop has been rotated slightly; the angle between the mean initial .04 and terminal .04 vectors is still diagnostically wide, but there is no longer a Q wave in lead I, and the Q wave in aV_L is only .02 sec. in duration.

subendocardial conduction network are involved. Therefore, the epicardium overlying the infarct is the last region of the ventricles to be depolarized, and the vectors from this region tend to dominate the last part of the QRS interval. When the initial and the terminal QRS deformities of infarction are plotted on the triaxial reference figure, they tend to be relatively opposite to one another in direction. The initial forces point away from the site of infarction and the terminal forces point toward the site of infarction. The mechanism of peri-infarction block and the way in which anterolateral peri-infarction block produces *LAD* are shown in the upper part of figure 4; a case illustrating this syndrome is shown later in figure 8.

From table 1 it can be seen that there were 160 cases of proved infarction among the 672 cases of this series. Forty-seven of the 160 cases had initial QRS changes of antero lateral infarction and 34 or two thirds of thes had *LAD*. On the other hand, only 20 o less than a fifth of the remaining cases o infarction had *LAD*, and only one tenth o the 512 cases in whom no infarction wa found at autopsy had *LAD*. These data emphasize both the high incidence of termina QRS abnormalities of the peri-infarctio block type in anterolateral infarction and th importance of myocardial infarction as a cause of *LAD*. In this series, over one third of all cases of *LAD* occurred in cases with infarction at autopsy.

The striking electrocardiographic feature of the *LAD* that occurs in anterolateral peri-infarction block is the wide angle between the initial QRS forces and the terminal QRS forces. To define this more precisely, the angle formed by the mean of the vectors generated during the first .04 sec. of the QRS interval (the "initial .04 vector") and the mean of the vectors generated during the remainder of the QRS interval (the "terminal .04 vector") exceeded 110° in all of these cases. On the other hand, among the 77 cases in this series with *LAD* but no evidence of infarction at autopsy there were only 5 with as wide an angle between initial and terminal .04 vectors. Two of these had advanced pulmonary disease with thoracic deformity; the role of pulmonary disease in producing *LAD* of this type will be explored later. The other 3 cases were all instances of marked left ventricular hypertrophy, 2 due to aortic stenosis and 1 to arterial hypertension with total heart weights of 650, 880, and 1050 Gm. respectively. Although an infarct may have been overlooked in these cases (they all had moderately advanced coronary artery disease), it is also possible that, as pointed out earlier, the fibrosis that accompanies marked left ventricular hypertrophy produces a conduction defect in the wall of the left ventricle with leftward deviation of the terminal QRS vectors similar to that seen in anterolateral peri-infarction block. In conclusion, anterolateral infarction with peri-infarction block is by far the commonest cause of *LAD* with a wide angle between initial and terminal QRS

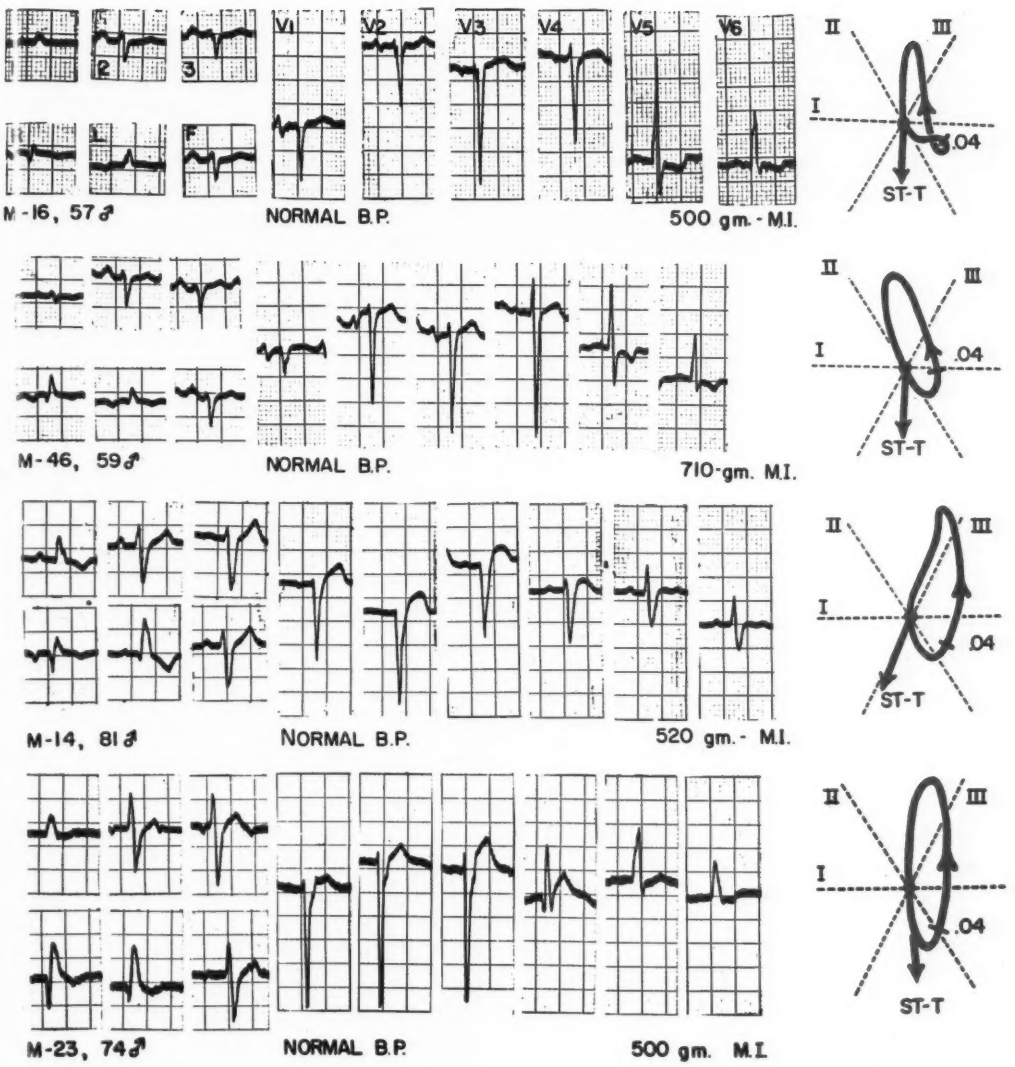

FIG. 5. Four cases with diagnostically wide angles between initial and terminal QRS vectors but no diagnostic "Q wave" patterns. At autopsy all 4 had gross myocardial infarction. The frontal plane QRS loops were constructed from the standard and unipolar limb leads for each case. The direction of the instantaneous vector at .04 sec. of the QRS interval is shown on each loop.

forces; if severe pulmonary disease or advanced left ventricular hypertrophy can be ruled out, it appears to be relatively diagnostic of infarction.

Might there not be cases of infarction with this wide angle but without diagnostic Q waves in any of the conventional leads because of a slight rotation of the entire QRS electric field? For example, suppose the QRS forces (fig. 4*A*) were rotated slightly leftward without changing their relationship to one another, as in *B*; now the wide angle between initial and terminal forces is still present, but no Q waves of .04 sec. are written in any of

the standard or unipolar limb leads. That this can happen is shown in figure 5. Here are 4 cases that proved to have infarctions at autopsy. They all show the diagnostically wide angle between initial and terminal .04 vectors yet have no diagnostic Q waves in any of the limb or precordial leads. (Perhaps the Q wave in Lead aV_L and in V_4 in the fourth tracing would, for many electrocardiographers, be diagnostic of infarction).

These 4 cases illustrate a type of QRS deformity diagnostic of infarction that has not been previously recognized; in addition, they emphasize the shortcomings of "Q-wave" criteria for the QRS diagnosis of in-farction. It is not generally realized that all patients, whether normal or not, have areas on the chest where Q waves of .04 sec. dura-tion can be recorded.[2] The diagnostic value of Q waves lies not in the Q wave itself but in the location of the lead that recorded it, and this is a function of the direction of the initial QRS electric forces. These cases demonstrate that occasionally the initial QRS forces can be diagnostically abnormal in direction yet not produce "diagnostic" Q waves in any of the conventional leads.

But the value of vector methods in clinical

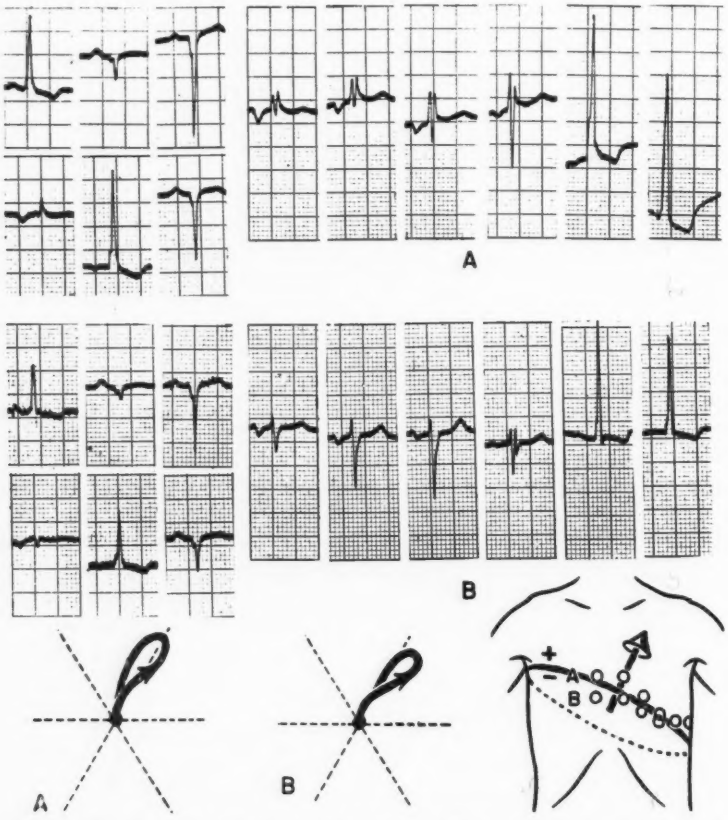

FIG. 6. Diaphragmatic infarction with *LAD* of terminal QRS forces identical with and probably due to peri-infarction block of the anterolateral type. *A* and *B* are 2 of several tracings illustrating apparent "coming and going" of R′ deflections at V_1 to V_3. The direction for the mean vector for the last .04 sec. of the QRS interval has been plotted from the conventional leads at the lower right. It can be seen that the reason for the inconstancy of the R′ deflections is variation in electrode location. For certain tracings the electrodes lay in the region of electric positivity (tracing *A*), while for others they lay in the region of electric negativity for this electric force (tracing *B*).

electrocardiography is to discriminate and clarify "pattern" criteria, not to supplant them. It is likely that cases of infarction such as these were not recognized previously because the alterations in the deflections were too complex to be recognized by QRS "patterns." However, when the abnormality of electric forces for a given syndrome is known, it is quite simple to describe "pattern" criteria for its recognition. These cases are characterized by an initial R wave of over .04 sec. followed by a deep S wave in lead aV_F and associated with marked *LAD* sufficient to produce a prominent terminal R wave on aV_R or even an S wave in lead I. But plotting the initial and terminal .04 vectors may still be necessary to be certain of the abnormality in a given case.

It will be recalled that *LAD* occurred with other types of infarction in addition to anterolateral. There were 113 cases of proved infarction with QRS deformity other than that of anterolateral infarction, and 20 had *LAD*. In several, the *LAD* was probably due to the same mechanism that produces *LAD* in anterolateral infarction. For example, the anatomic location of the electric defect in strictly anterior infarction is quite near that of anterolateral infarction (fig. 1), and 5 of the 18 cases of this type had *LAD*. Similarly 4 of the 16 cases of apical and strictly posterior infarction had *LAD*. In addition, since in most cases of fatal infarction there is more than 1 infarct at autopsy, it is possible that in certain cases the deformity of the initial .04 sec. will be dominated by an infarct at one region while the deformity of the terminal .04 sec. may be dominated by an infarct at another region. Perhaps this combination accounts for the *LAD* in others of these cases.

In cases of infarction with terminal QRS deformity similar to that of anterolateral infarction but initial QRS deformity of some other electric location, the angle between the initial .04 vector and the terminal .04 vector may not be abnormal. For example, in diaphragmatic infarction with *LAD*, the initial and terminal .04 vectors are relatively parallel, (*see* fig. 6). Under these circumstances the recognition of infarction and its differentiation from uncomplicated *LAD* may be quite difficult. As will be seen later, the somewhat anterior direction of the terminal vector in this case (producing an R-prime at V_1 and V_2) supports the likelihood that the *LAD* is due to peri-infarction block.

Other Causes of Left Axis Deviation

Among the 131 cases of *LAD* of all causes in this series, there were 23 with no evidence of infarction at postmortem examination and with hearts weighing 400 Gm. or less. In 6 of these the important postmortem finding was severe pulmonary disease, either pulmonary emphysema or pulmonary fibrosis, with right ventricular hypertrophy and, in 2 cases, associated kyphoscoliosis. That advanced pulmonary disease may occasionally produce marked *LAD* has been noted in the literature previously.[10-13] It is possible that the *LAD* is due to some myocardial factor unrelated to the pulmonary disease. However, such a factor was not apparent from the autopsies in these cases. Two of the 6 subjects were less than 50 years of age and 1 was female, which makes it unlikely that the *LAD* was due to the effects of chronic coronary artery disease. A more likely explanation, although entirely conjectural, suggests that *LAD* may be related to the reduced electric conductance of the lung in advanced pulmonary disease. It has been shown that the electric conductance of normal pulmonary tissue is not greatly different from that of other tissues.[14] The electric conductance in the emphysematous lung has not been tested; however, in view of the presence of large nonconducting air sacs in the lung in this disease, it may well be greatly reduced. If this were so, the electric field surrounding the heart would be altered; the lead-field lines for leads II and III would in effect be concentrated vertically in the mediastinum, and the limb leads would now record principally the superiorly and inferiorly directed components of the electric forces of the heart. For example, QRS forces directed toward the left flank would be recorded as strictly vertically directed, while forces directed toward the left arm would be

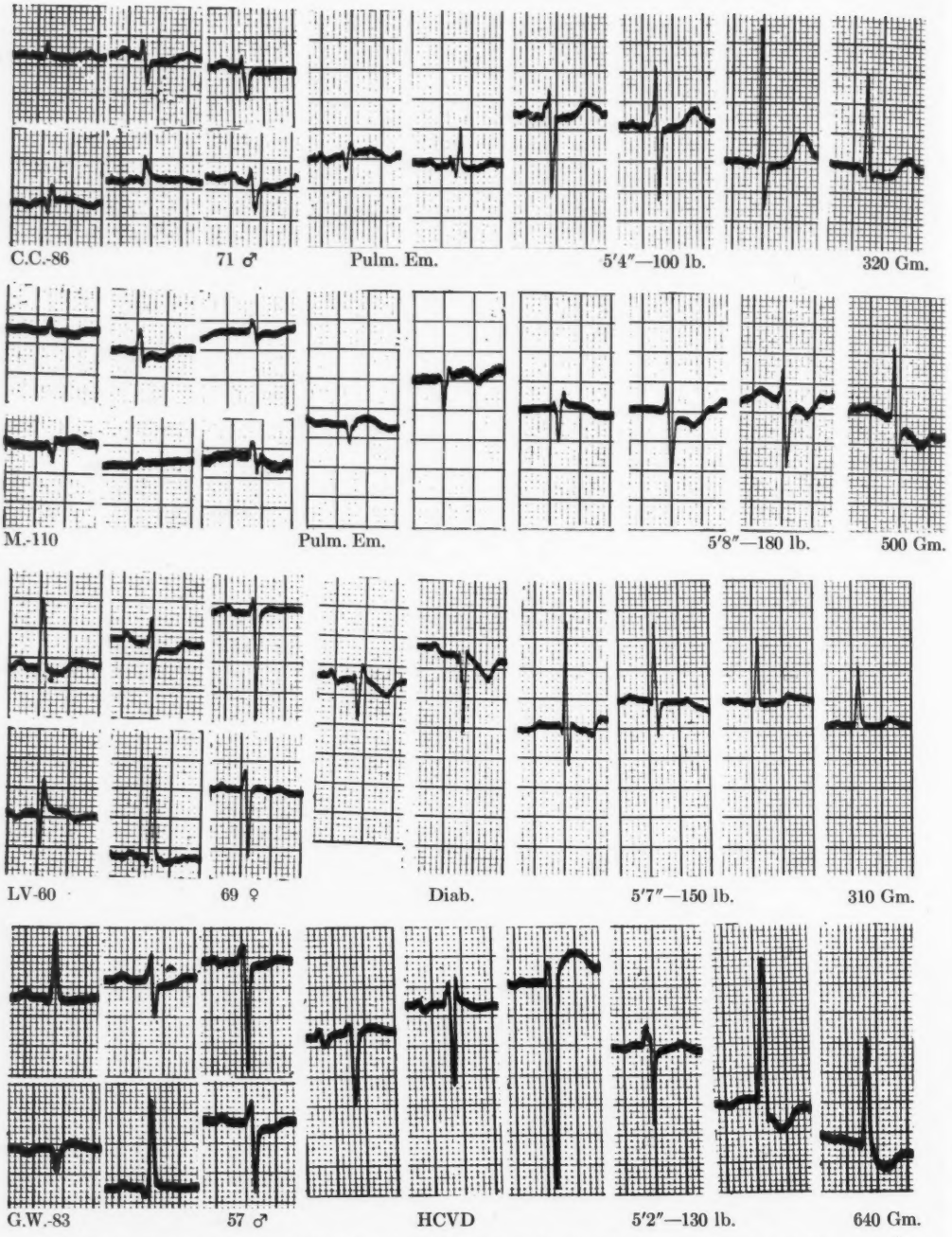

FIG. 7. Four cases with *LAD* of terminal QRS forces; the terminal forces are also slightly anteriorly directed in each case producing terminal R′ deflections in the certain of the precordial QRS complexes. The upper 2 cases are instances of severe pulmonary disease, the third of chronic coronary artery disease, and the fourth of hypertension with left ventricular hypertrophy.

recorded as strictly superiorly directed. With just slight differences in the anatomic position of the heart or slight variations in the magnitude of either the initial QRS forces or the more leftward terminal QRS forces in patients with emphysema, the limb leads would record mean QRS axes that are either strictly inferior or strictly superior in direction and rarely in between. Two cases with markedly leftward terminal forces due to severe pulmonary disease are shown in figure 7. To be sure, *LAD* was not the typical axis direction for cases of pulmonary disease in the series as a whole; there were 27 other cases with severe pulmonary disease and right ventricular hypertrophy at autopsy, and all these had the more familiar vertical QRS axis.

Excluding these cases of *LAD* due to pulmonary disease, there were 17 cases of *LAD* with normal heart weights and no evidence of infarction at autopsy. What was the mechanisms of the *LAD* in these cases? All 17 had abnormally directed T vectors and two-thirds had ST and T vectors characteristic of what is called left ventricular "strain" as defined earlier. On the other hand, among 395 cases with normal heart weights and no evidence of infarction at postmortem examination but with normal QRS axis directions, only 5 had ST and T vector alterations characteristic of left ventricular "strain." The high incidence of abnormalties in repolarization in the cases with *LAD* indicates that the T abnormality is intrinsically related to the *LAD*. This relationship suggests that the *LAD* may represent a conduction defect peripherally in the wall of the left ventricle with "secondary" T-vector alterations. It has been pointed out that uncomplicated *LAD* is exceedingly uncommon among subjects under 40 years of age.[15] Although the number of cases of this type of *LAD* in the present series is small, their mean age was considerably higher than that of the series as a whole. For these reasons, it is concluded that *LAD* in older subjects without evidence of infarction or severe pulmonary disease is probably due to "parietal block" secondary to the myocardial fibrosis of chronic coronary artery disease. It is analogous, perhaps, to the mechanism of the *LAD* seen in peri-infarction block and in certain cases of left ventricular hypertrophy described earlier.

Might not the *LAD* in these cases and in the cases of *LAD* associated with left ventricular hypertrophy be due to incomplete left bundle-branch block? This view also would explain the high incidence of ST and T abnormalities in these cases. However, there are 2 cogent reasons for suspecting that this is not the case. In the first place, it has been shown by several investigators that when complete left bundle-branch block develops, there is usually no change in the direction of the mean QRS axis.[16, 17] One would expect that this would also be the case for incomplete left bundle-branch block. Under these circumstances, one would still need an explanation for the *LAD* that preceded the bundle-branch block in these cases. In the second place, to prove that left bundle-branch block (either complete or incomplete) has taken place one must have a control tracing showing normal ventricular conduction recorded shortly before or after the tracing with the conduction defect. By comparing the 2 tracings one can prove that (1) the QRS alteration was sudden in onset, (2) the mode of entrance of excitation into the left ventricle was altered (as shown by a change in the directions of the initial QRS forces), and (3) infarction was not responsible for the alteration in initial QRS forces. These features must be demonstrated if a given QRS syndrome is to be attributed to a lesion in the main branch of the left bundle. (In incomplete left bundle-branch block the QRS interval must be prolonged to .09 to .11 sec. with appropriate changes in ST and T vectors, while for complete left bundle-branch block the prolongation is to .12 sec. or more). Cases with tracings showing normal ventricular conduction before and after complete left bundle-branch block fulfilling these criteria are not uncommon.[18] On the other hand such cases are exceedingly rare among those called incomplete left bundle-branch block. In a search among 1000 cases with tracings labeled "incomplete left bundle-branch block," "left ventricular strain," or "left ventricular con-

duction defect" in several different hospitals, not a single case was found that fulfilled these criteria. Only 1 such case has been found in the literature, and here it is difficult to be sure that the initial QRS forces were altered in direction when the QRS complex change took place.[19] It is concluded that what is called incomplete left bundle-branch block is an exceedingly uncommon conduction defect and not likely to have been the cause of the *LAD* in any of the cases in the present study. *LAD* of the type under consideration tends to develop gradually over a period of years with no certain change of initial QRS forces and, also unlike bundle-branch block, seems never to return to normal.

R′ Deflections in the Precordial Leads in the Presence of Left Axis Deviation

In current electrocardiographic practice an R′ deflection in V_1 or V_2 is generally attributed to right bundle-branch block if the QRS interval is prolonged, and to right ventricular hypertrophy if the QRS interval is normal, regardless of the direction of the mean QRS axis. However, from time to time the direction of the mean QRS axis is inconsistent with the precordial lead findings, giving rise to such ambiguities of nomenclature as "left bundle-branch block masquerading as right bundle-branch block," or "left bundle-branch block with right axis deviation."[20, 21] This method for interpreting the precordial leads R′ deflection resulted from the assumption that a given unipolar lead was recording principally the electric events from the region of the heart immediately underlying it. From this point of view, an R′ deflection in the right precordial leads meant that the last region of the heart to be depolarized was the right ventricle, since this lay immediately beneath the V_1 and V_2 electrodes. However, the evidence is now quite conclusive that body surface unipolar leads are more nearly recording the resultant electric activity of all regions of the heart than of the immediately underlying region.[14] In other words, for practical clinical purposes, all electrode locations can be considered to be recording from essentially the same central resultant electric forces. This means that in interpreting the R′ deflection in the right precordial leads one must take into consideration the terminal deflections of the QRS complexes in all leads of the clinical tracing. The simplest method for doing this is to base the interpretation on the direction of the terminal QRS vectors. As the cases in this study show, occasionally R′ deflections are written at V_1 and V_2 by QRS forces that can be attributed to the right ventricle only by assuming the most extravagant and improbable torsion of the heart anatomically from its normal position.

The terminal QRS vector alterations responsible for the R′ deflections at V_1 and V_2 in the presence of QRS prolongation to .12 sec. or more have been discussed previously.[18] We are here concerned with those associated with a QRS interval that is normal or only slightly prolonged. Such R′ deflections can be seen with 3 different directions of the terminal QRS vectors and the mechanism and clinical implications of each are different. 1. R′ deflections in the right precordial leads are seen when the terminal QRS forces are directed inferiorly, slightly rightward and anteriorly, producing an $S_1R_2R_3$ pattern in the standard limb leads. This is an appropriate direction for an electric force generated from the right ventricle, and since all cases in the present series with this pattern in the limb and precordial leads had pathologic findings consistent with right ventricular hypertrophy, it can be concluded that this is usually its cause. 2. R′ deflections at V_1 and V_2 are also seen when the terminal QRS forces are directed rightward, superiorly and slightly anteriorly, producing the $S_1S_2S_3$ pattern. Although most commonly seen in patients with cor pulmonale, this pattern may occur in young adults with no evidence of heart disease and is occasionally acquired as a part of the QRS deformity of infarction.[2] It is likely, therefore, that it is due to a right ventricular conduction defect, perhaps in the region of the crista supraventricularis of the right ventricle.[24] 3. R′ deflections at V_1 and V_2, or both, are seen with terminal QRS forces directed superiorly and leftward, producing

an $R_1S_2S_3$ pattern in the limb leads. There is no region of the right ventricle facing in this particular direction, and it is extremely unlikely that they are right ventricular forces.

The terminal forces in a given case of *LAD* with R′ deflections in precordial leads may have any of these 3 directions. However, in this study we are concerned only with the cases of the third type; that is, terminal forces directed leftward and superiorly, producing the $R_1S_2S_3$ pattern in the limb leads. It can be seen in table 1 that there were 46 cases with terminal R′ deflections at V_1 or V_2, or both, in the entire series. In 15 of the 46 cases the terminal QRS forces were of the third type mentioned above. Eight, or half of these 15 cases, had myocardial infarction at autopsy; and all 8 showed anterolateral or strictly anterior infarction with marked *LAD* of the mean QRS axis. Therefore, it is probable that all 8 were examples of anterolateral peri-infarction block. Thus, the commonest cause of an R′ deflection in the right precordial leads in association with *LAD* of terminal QRS forces is peri-infarction block. Cases illustrating this have been published by others.[20, 25, 26]

Whenever the terminal QRS forces are leftward in direction, as is the case in anterolateral peri-infarction block, there is always an area on the upper left chest where unipolar leads will record positivity for the last part of the QRS complex. Whether or not this area of terminal positivity will extend down far enough on the anterior chest to include the region where the conventional precordial electrodes are placed depends upon how far anteriorly the leftward terminal forces are directed. The distribution of terminal positivity on the chest in such a case is shown in figure 8. Since only 1 in 5 cases of anterolateral peri-infarction block shows terminal R′ deflections in the precordial leads, it appears that the area of positivity for these terminal QRS vectors is near, but does not often include the region of the chest where the precordial leads are placed in these cases. However, the region of positivity for these leftward terminal forces is usually so near the location of the precordial leads that slight variations in the placement of precordial electrodes in a given case may cause the R′ deflection to come and go from tracing to tracing. Figure 6 illustrates such a case; the terminal R′ deflection was present in the precordial leads in some tracings and absent in others. It can be seen that for certain of the tracings, the electrodes for V_1 and V_2 lay in the area of relative positivity for terminal QRS vectors, writing terminal R waves, and for others they lay in the area of relative negativity for the vector, writing terminal S waves. When the terminal QRS vector is not sufficiently anteriorly directed to produce R′ deflections in the precordial leads, a shallow notch on the ascending limb of the S wave instead of an R′ wave may be seen in the precordial leads. How this can take place may be seen by studying figure 8. Cabrera and Friedlander[25] have also called attention to this shallow notching of the S wave in the precordial leads as a sign of infarction.

Among the 15 cases of *LAD* with terminal R′ deflections at V_1 and V_2 due to leftward and superiorly directed terminal QRS forces ($R_1S_2S_3$) there were 2 cases with severe pulmonary disease, no evidence of myocardial infarction, and normal heart weights. A possible explanation for the *LAD* in these cases has already been suggested. It is well to remember that verticalization of the QRS forces by pulmonary emphysema will apply to rightward forces as well as to leftward forces. Possibly these 2 cases represent verticalization of anteriorly directed $S_1S_2S_3$: forces which, as mentioned earlier, are commonly seen in the presence of chronic cor pulmonale.

Of the remaining 5 cases with *LAD* and R′ deflections in the right precordial leads, 2 had normal heart weights and no evidence at autopsy of either pulmonary disease or myocardial infarction, and 3 were instances of marked left ventricular hypertrophy. One of each of these is shown in figure 7. It is generally accepted that uncomplicated left ventricular hypertrophy causes the terminal QRS forces to be more posteriorly directed than normally (as evidenced by the shift of QRS transition to the left).[8] The fact that the terminal forces were more anteriorly directed

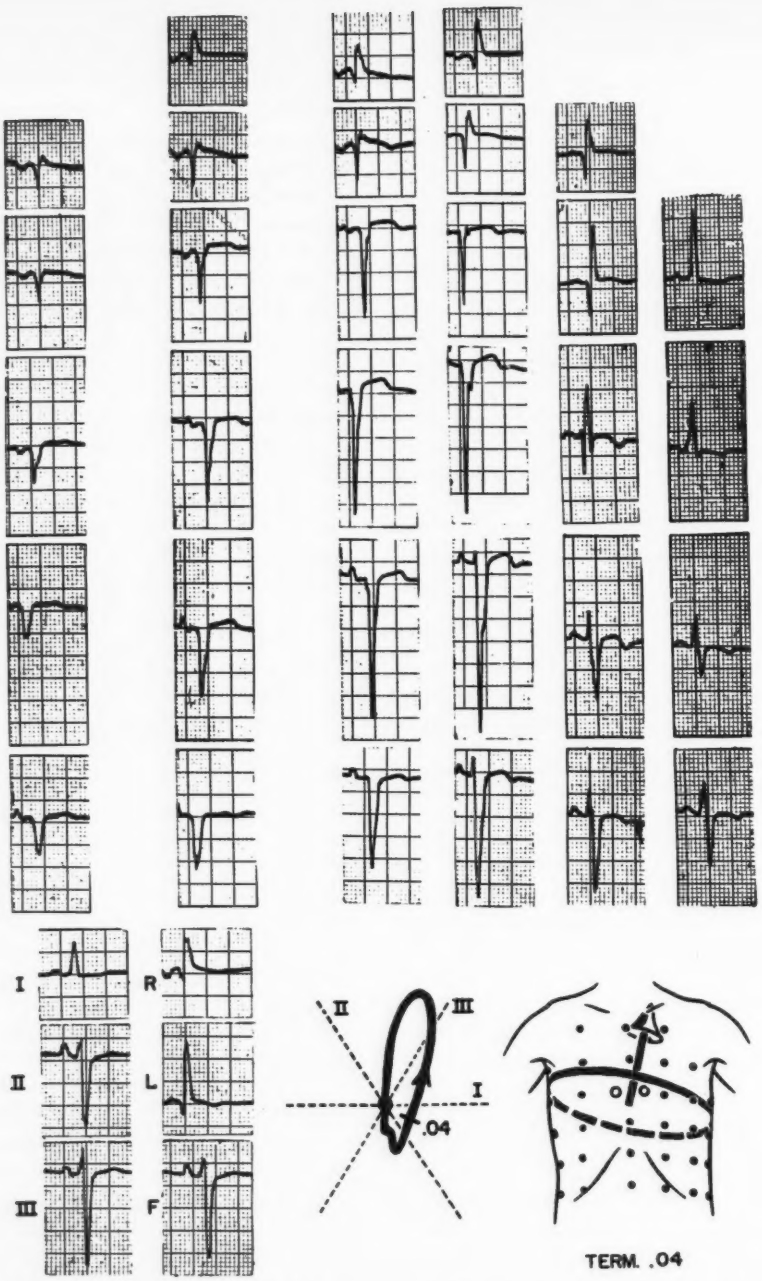

FIG. 8. Unipolar lead QRS complexes in a case of *LAD* due to anterolateral peri-infarction block. The unipolar deflections were recorded from a number of points on the anterior surface of the chest indicated by the solid dots on the torso at lower right. The location of the electrodes for V_1 and V_2 are shown by open circles on this figure. The null contour and direction for the mean vector for the last .04 sec. of the QRS interval, shown on the torso, were plotted from the chest unipolar deflections. They indicate the distribution of positivity and negativity on the chest for the terminal part of the QRS complex. The electrode locations for the conventional precordial leads lie in the area of electric negativity for the terminal .04 sec. vector. However, they are near the null contour for this force, explaining why the terminal S waves would be shallow in the conventional precordial leads. Had the conventional precordial leads been recorded slightly higher on the chest, terminal R waves would have been recorded in the QRS complexes for these leads.

than normally in these 3 cases is further evidence that the *LAD* of left ventricular hypertrophy is due to a conduction defect.

In the summary, the analysis of the incidence of R′ deflections in the precordial leads in subjects with *LAD* has disclosed another electric similarity between the *LAD* of anterolateral peri-infarction block, the *LAD* of marked left ventricular hypertrophy, and the *LAD* of chronic coronary artery disease: they all may be associated with terminal QRS forces that are directed sufficiently anteriorly to cause R′ deflections to appear at V_1 or V_2. This finding adds further evidence to the likelihood that the *LAD* for each is due to a conduction defect distal in the conduction network of the left ventricle, a sort of "parietal block."[6, 7] The fact that the terminal forces are more commonly directed anteriorly in cases of peri-infarction block than in either of the other 2 syndromes is useful from a clinical point of view and also suggests that the similarity of the *LAD* in these 3 syndromes is a superficial and strictly electrocardiographic one. The underlying electrophysiologic abnormality may well be quite different in the 3 syndromes; but too little is known of the left ventricular conduction mechanism in man to permit further speculation.

Summary and Conclusions

Six hundred seventy-two consecutive cases in which an electrocardiogram had been recorded within 5 weeks of death and in which detailed postmortem examination had been performed are the basis of this report; those under the age of 30 years and those with QRS interval duration of .12 sec. or more have been excluded.

One third of all cases with left axis deviation had myocardial infarction at autopsy. Of 160 cases of proved infarction, 67 had left axis deviation and two thirds of these had the QRS deformity of anterolateral infarction. Thus, left axis deviation is considerably more common in anterolateral infarction than in any other type of infarction or in any other single category of heart disease. The mechanism of the left axis deviation in this type of infarction is shown to be peri-infarction block, characterized by a diagnostically wide angle between the initial and the terminal QRS forces. Four cases are shown with proved infarction in which this angle was diagnostically wide but in which there were no diagnostic "Q waves" in any of the conventional leads. This is an electrocardiographic pattern of infarction that has not been previously recognized.

Left axis deviation was seen in less than half of the cases with proved left ventricular hypertrophy. Neither the severity of the hypertrophy, nor the anatomic position of the heart in the chest, nor the body build of the patient plays a significant role in the development of left axis deviation in these subjects. Incomplete left bundle branch block is an extremely rare cause of left axis deviation in these or other cases. Left axis deviation of left ventricular hypertrophy represents a type of "parietal block" in the more distal parts of the left ventricular conduction network and is perhaps the result of the myocardial fibrosis that accompanies marked left ventricular hypertrophy.

Seventeen subjects with no evidence of myocardial infarction or left ventricular hypertrophy at autopsy had marked left axis deviation. The relatively advanced average age of these patients and the presence of myocardial fibrosis in the majority of them suggest that this is due to a conduction defect similar to that seen in left ventricular hypertrophy and related perhaps to the chronic coronary artery disease that was present. Six cases with severe pulmonary disease had marked left axis deviation, possibly due to "verticalization" of the electric field of the heart by the reduced electric conductance of the emphysematous lung.

Among 15 cases with *LAD* and R′ deflections in precordial leads V_1 and V_2, over half were instances of anterolateral peri-infarction block, and this appears to be the commonest cause of R′ deflections in the precordial leads in *LAD*. The remaining cases were equally divided among cases of severe pulmonary disease, cases of left ventricular hypertrophy, and elderly patients with chronic coronary artery disease.

That the terminal QRS forces can occasionally be somewhat anteriorly directed in cases of left axis deviation due to left ventricular hypertrophy or chronic coronary artery disease, is considered further evidence that the left axis deviation in these cases is due to a parietal block in the left ventricle, analogous to that seen in anterolateral peri-infarction block.

Acknowledgment

The author wishes to acknowledge the generous assistance of Dr. Frederic T. Kirkham, Dr. Philip Paty, and Dr. Edward Frohlich in certain phases of this study.

Summario in Interlingua

Le base del presente reporto es 672 casos consecutive in que electrocardiogrammas habeva essite obtenite intra 5 septimanas ante le morte e in que protocollos autoptic esseva disponibile. Casos de patientes de infra 30 annos e de patientes con intervallos QRS de un duration de 0,12 sec o plus habeva essite excludite.

Un tertio de omne casos con deviation axial sinistrorse involveva constatationes autoptic de infarcimento myocardial. De 160 casos demonstrate de infarcimento, 67 habeva deviation axial sinistrorse, e duo tertios de istos habeva le deformitate de QRS que es characteristic de infarcimento anterolateral. Ergo, deviation axial sinistrorse es considerabilemente plus frequente in infarcimento anterolateral que in ulle altere typo de infarcimento o in ulle altere categoria individual de morbo cardiac. Es monstrate que le mechanismo del deviation axial sinistrorse in iste typo de infarcimento es un bloco peri-infarcimental, characterisate per un diagnostic angulo obtuse inter le fortias de QRS initial e terminal. Es signalate 4 casos de infarcimento demonstrate in que iste angulo esseva diagnosticamente obtuse sed in que nulle del derivationes conventional monstrava diagnostic "undas Q." Isto es un configuration electrocardiographic de infarcimento que ha non previemente essite recognoscite.

Deviation axial sinistrorse esseva notate in minus que un medietate del casos con demonstrate hypertrophia ventricular. Ni le severitate del hypertrophia ni le position anatomic del corde intra le thorace ni le conformation corporee del patiente ha un rolo significative in le disveloppamento de deviation axial sinsitrorse in iste subjectos. Incomplete bloco de branca sinistre es un causa rarissime de deviation axial sinistrorse in tal o altere casos. Deviation axial sinistrorse de hypertrophia sinistro-ventricular representa un typo de "bloco parietal" in le portion plus distal del rete de conduction sinistro-ventricular e es forsan le resultato del fibrosis myocardial que accompania marcate hypertrophia sinistro-ventricular.

Dece-septe individuos sin evidentia autoptic de infarcimento myocardial o de hypertrophia sinistro-ventricular habeva marcate grados de deviation axial sinistrorse. Le relativemente alte etate median de iste patientes e le presentia de fibrosis myocardial in le majoritate de illes pare indicar que isto es debite a un defecto de conduction simile al defecto observate in hypertrophia sinistro-ventricular e relationate, forsan, al presentia de chronic morbo de arteria coronari. Sex casos con sever morbo pulmonar habeva marcate deviation axial sinistrorse, possibilemente in consequentia de "verticalisation" del campo electric del corde per le reducite conductantia del pulmone emphysematose.

Inter 15 casos con *LAD* con deflexiones de R′ in le derivation precordial V_1 e V_2, plus que un medietate esseva casos de bloco peri-infarcimental anterolateral. Iste bloco appareva le plus communmente causa de deflexioner de R′ in le presentia de deviation axial sinistrorse. Le remanente casos representava in numeros equal sever morbo pulmonar, hypertrophia sinistro-ventricular, e patientes de etate avantiate con chronic morbo de arteria coronari. Le facto que le terminal fortias de QRS in casos de deviation axial sinistrorse es a vices orientate levemente in un direction anterior, debite a hypertrophia sinistro-ventricular o chronic morbo de arteria coronari, es considerate como un proba additional que le deviation axial sinistrorse in iste casos es causate per un bloco parietal in le ventriculo sinistre, de maniera analoge a lo que es incontrate in bloco peri-infarcimental anterolateral.

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An Evaluation of Starr's Equation for the Prediction of Stroke Volume

By Travis Bridwell, Rachel M. Jenss, Sc.D., and David G. Greene, M.D.

Starr's formula for deriving stroke volume from pulse pressure, diastolic pressure, and age has been tested experimentally in a group of miscellaneous hospital patients. Nearly simultaneous measurements of stroke volume by the direct Fick method and of brachial arterial pressure by direct puncture were analyzed. The measured stroke volume frequently differed considerably from the values calculated from the formula. Certain theoretic limitations of the application of multiple regression equations to this material are presented.

THE determination of cardiac stroke volume by the Fick principle is a laborious procedure. If this important physiologic datum could be obtained more simply and still retain the accuracy of the Fick technic, such simplification would be of benefit to the physician. Starr, Schnabel, Askovitz, and Schild[1] attempted to predict stroke volume with a multiple-regression-type mathematical equation. Simulating 46 systoles with known stroke volumes in 6 cadavers, they recorded simultaneous intra-arterial pressures. Employing 5 measurements, 61 equations were derived to determine which combination of measurements gave the smallest error of prediction.* These measurements included diastolic pressure, pulse pressure, pulse wave velocity, body surface, and age. The equation that gave the smallest error included pulse pressure (*PP*), diastolic pressure (*DP*), and age, as follows:

$$\text{Stroke volume} = 91.0 + 0.54\ PP - 0.57\ DP - 0.61\ age$$

In two thirds of the estimates with this equation the error was less than 5.9 ml. Jackson[2] has devised a nomogram for the easy application of this formula to patients.

A priori it would seem that mathematical manipulation of systoles simulated in cadavers is far removed from the determination of a dynamic quantity like cardiac stroke volume in the living subject. The present analysis was undertaken to test the validity of this procedure.

Methods and Results

Data were collected on 28 miscellaneous hospitalized patients in whom stroke volume was measured by means of the Fick principle and right-sided cardiac catheterization. Each patient was in a resting state. Two stroke volume determinations were conducted 20 min. apart. The average difference between the 2 determinations of stroke volume was 7.1 ml., or less than 12 per cent of the mean stroke volume for the whole group of 60 ml. There was a variance of the difference of 6.7 ml. For each determination duplicate intra-arterial pressures were recorded photographically with a Hathaway blood pressure recording system. Subjects ranged in age from 23 to 72 and exhibited varying disease states. Included were 11 with chest disease, of whom 6 had cor pulmonale, 5 with rheumatic heart disease, 4 with arteriosclerotic heart disease, 3 with hypertensive cardiovascular disease, 4 with normal cardiovascular systems, and 1 with thyrotoxicosis. It is in such miscellaneous patients that an easy determination of stroke volume would be most helpful.

Starr's equation was applied to our data. Since duplicate pressure readings had been taken for each stroke-volume determination the equation was applied to each of these 104

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* In these computations the equation of the best line is found by the method of least squares. The error of this method, as defined by the standard error, can be readily computed.

readings. A standard error of 24.0 ml. was obtained from the line of perfect agreement when Starr's equation was applied to our data. This compares with his predicted error of 5.9 ml.

Another approach was to derive our own equation from our own data. The method of least squares presented by Mills[3] was used. This method assumes all the error to be in the dependent variable and none in the independent variables. The equation derived from our data is:

$$\text{Stroke volume} = 66.0 + 0.34\ PP - 0.11\ DP - 0.36\ age$$

The standard error of our own equation as applied to our own data was 24.3 ml.

Discussion

Of the many influences on stroke volume one would expect age to be one of the least important. Diastolic pressure also bears no immediately obvious relation to stroke volume. It is therefore not surprising that formulas based on these 2 variables do not predict stroke volume well. Since neither Starr's equation nor one similarly derived by us yields useful predictions of stroke volume in a representative cross section of patient population, the further pursuit of this subject does not appear profitable.

There is, however, the additional question of statistical theory. It is not so much a matter of taking data and running them through an equation as it is deciding whether or not it is correct to use a multiple regression equation. Multiple-regression analysis is a statistical tool that enables one to study the effect of multiple, independent variables upon a dependable variable. What Starr and his group have done is to take 5 factors—diastolic pressure, pulse pressure, pulse wave velocity, body surface area, and age—and derive 61 multiple-regression equations by using these factors in all possible combinations. They found that the equation with pulse pressure, diastolic pressure, and age provided the best basis for the most accurate estimation. The criterion by which they judged the worth of the various equations was the standard error of the line of best fit according to the method of least squares.

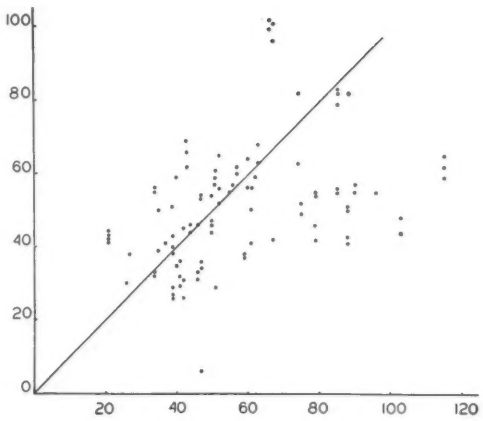

Fig. 1. Comparison of stroke volume obtained by the direct Fick method (abscissa) and by Starr's formula (ordinate). The solid line indicates perfect agreement.

A standard error in and of itself may be misleading over a wide axis. It is conceivable that there might be ranges of stroke volumes where close agreement existed between the actual and estimated stroke volumes. In such an instance an estimating equation would still have value. To see whether this was true a graph was made to compare actual and estimated stroke volume (fig. 1). The disparity between actual and estimated values is apparent. Inspection suggests that the data come from 2 overlapping populations with 2 separate regressions. The cases have been examined with this in mind, and no correlation with other known characteristics has been discovered.

The use of multiple-regression equations is based upon several assumptions that must be satisfied for the results to be valid.[4] An important requisite is that each independent variable be linearly related to the dependent variable. For example, in order to include age in the equation, stroke volume must either increase or decrease linearly as age increases. Just from an empiric basis it is hard to imagine that a linear relation exists between stroke volume and age.

From our data diastolic pressure, pulse pressure, and age were plotted against stroke volume (figs. 2–4). It is apparent from these figures that a linear relation does not exist.

A second fault in the equation is that the 3

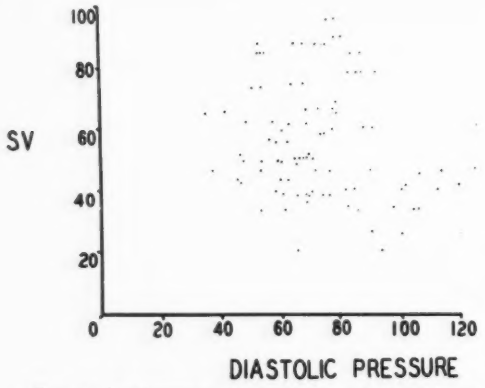

FIG. 2. Scattergram showing the relationship of stroke volume (*SV*) in ml. obtained by the direct Fick method, with the diastolic pressure in mm. Hg obtained from graphic records. Each dot represents 1 pair of observations. Note the absence of a linearity.

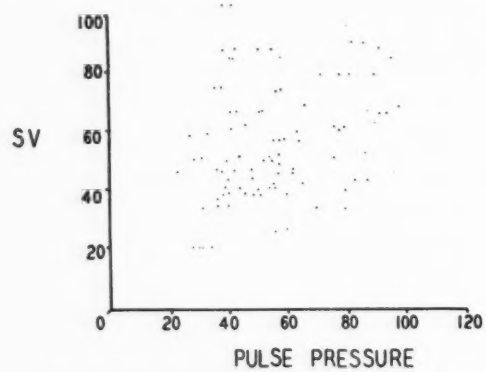

FIG. 3. Scattergram showing the relationship of stroke volume (*SV*) in ml. obtained by the direct Fick method with the pulse pressure in mm. Hg obtained from graphic records. Each dot represents 1 pair of observations.

"independent variables" are not independent of one another. Pulse pressure is defined as the difference between systolic pressure and diastolic pressure. Here pulse pressure is distinctly dependent upon the diastolic pressure, so that the equation does not really use 3 independent variables, but 2. A mistake in the determination of the diastolic pressure will influence the pulse pressure also.

If one overlooks the absence of linearity and the dependence of pulse pressure on diastolic pressure, the material may be examined on

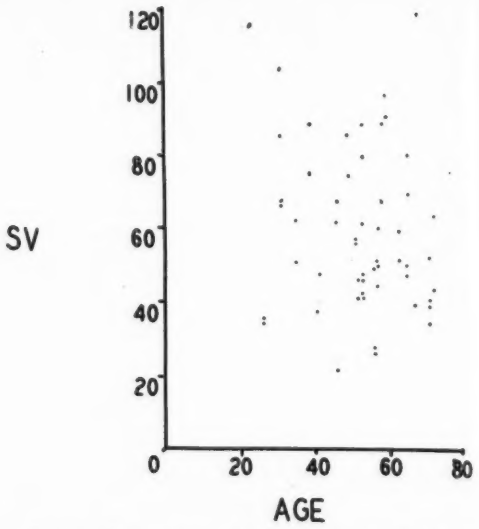

FIG. 4. Scattergram showing the relationship of stroke volume (*SV*) in ml. obtained by direct Fick method with age in years. Each dot represents 1 pair of observations. Note the absence of a linearity.

TABLE 1.—*Formulas for Prediction of Stroke Volume*

Starr and co-workers[1]	$SV = 91.0 + 0.54\ PP - 0.57\ DP - 0.61$ age
Present authors	$SV = 66.0 + 0.34\ PP - 0.11\ DP - 0.36$ age

TABLE 2.—*Coefficients of Formulas for Prediction of Stroke Volume*

	PP	*DP*	Age
(1) Starr and co-workers[1]	.54	.57	.61
(2) Present authors	.34	.11	.36
Ratio (per cent) $\frac{(2)}{(1)} \times 100$	63	19	59

other grounds. Comparison of Starr's equation and our own in tables 1 and 2 reveals what appear to be differences between the coefficients. One might expect closer agreement between the coefficients if Starr's fundamental idea was applicable to our data. Another interesting observation is that the same accuracy is achieved whether Starr's equation or our own equation is used on our data.

The stroke volumes in our group of subjects

ranged between 21 and 115 ml., with a median value of 56 ml. In dealing with a physiologic variable of this magnitude, an error of 5.9 ml. might be quite acceptable for many purposes. But an error of 24 ml. seems so large that it would be difficult to use such variable data.

Summary

The application of Starr's multiple-regression equation for the prediction of stroke volume to 104 intra-arterial pressures obtained from 28 resting patients resulted in a standard error of 24.0 ml. rather than the 5.9 ml. obtained by Starr. Application of an independently derived equation to our own data resulted in a standard error of 24.3 ml.

To employ a multiple-regression equation validly several conditions must be fulfilled, 1 of which is a linear relation between each independent variable (diastolic pressure, pulse pressure, and age) and the dependent variable (stroke volume). This requisite has not been satisfied in our data. It is apparent that Starr's equation is not sufficiently accurate to yield meaningful estimates of stroke volume in a heterogeneous group of hospital patients.

Summario in Interlingua

Le equation Starr a regression multiple pro le prediction del volumine pulsar esseva applicate a 104 pressiones intra-arterial obtenite ab 28 patientes in stato de reposo. Le resultante error standard esseva 24,0 ml plus tosto que le 5,9 ml obtenite per Starr. Le application de un equation de derivation independente resultava in un error standard de 24,3 ml.

Le uso valide de un equation a regression multiple presuppone le satisfaction de plure conditiones. Un de istos es le existentia de un relation linear inter cata un del variabiles independente (pression diastolic, pression pulsar, etate) e le variabile dependente (volumine pulsar). In nostre datos iste condition non esseva satisfacite. Il es clar que le equation Starr non es sufficientemente accurate pro le calculation de significative estimationes del volumine pulsar in un gruppo heterogenee de patientes hospitalisate.

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It is often difficult to determine by palpation whether a pulsating liver is due to tricuspid insufficiency, to the impact of the contracting right ventricle, or to the expanding subdiaphragmatic aorta. In the majority of instances, simple physical examination will make the correct diagnosis. The fingers of one hand are placed on a carotid artery, while the other hand presses gently upon the enlarged liver. If the pulsations are transmitted by a ventricular or aortic impact, both carotid and hepatic pulsations are felt to occur simultaneously; if due to tricuspid insufficiency, the hepatic pulsation is felt after the carotid pulsation, imparting a see-saw sensation to the examining fingers. The accuracy of this simple procedure has been checked by recording characteristic insufficiency pressure curves from the right atrium during cardiac catheterization in man and by postmortem examination.

Kitchell

Survival Rates after Acute Myocardial Infarction with Long-Term Anticoagulant Therapy

By JOHN W. KEYES, M.D., ELLET H. DRAKE, M.D., AND F. JANNEY SMITH, M.D.

Evidence is set forth to show the value of continuous long-term anticoagulant therapy by comparison with a control group of patients who have also had multiple coronary occlusions or single infarcts, followed by severe angina pectoris or episodes of coronary failure. Statistical life-estimate determinations are included. Bleeding complications are encountered less frequently with improved methods of management and are considered a justifiable risk, in view of the serious consequences of the natural progress of the disease. After a program of long-term anticoagulant treatment has been instituted, cessation of therapy may be hazardous.

THE value of anticoagulants in the treatment of the acute phase of myocardial infarction has been established by favorable reports from many clinics, although some difference of opinion exists regarding the selection of patients.[1, 2, 3, 6] To date, however, there have been but few reports of well-controlled studies in the use of the so-called "long-term" anticoagulant therapy. Although continuous protection from thromboemboli is desirable for all cases of coronary artery disease, particularly those with recurrent episodes of infarction, worthwhile evaluation cannot be obtained from following a small number of patients over a short period of time without adequate controls. In the series we are reporting, enough patients have been followed closely for 6 months to 5 years to allow statistically valid conclusions.

The cases given long-term therapy have been divided into 2 classifications. In the first or "single infarct group" are included those patients who have had a single myocardial infarction with transmural muscle damage. All have had satisfactory recovery from the acute phase (initial 6 weeks), but suffered recurring bouts of coronary failure or angina that did not respond to the conventional modes of therapy. In this respect they present a more serious prognosis than corresponding control patients that were unselected cases with single infarcts without regard to the subsequent occurrence of coronary pain. In the second or "recurrent infarct group" the patients had survived the acute phase of 2 or more well-substantiated episodes of acute myocardial infarction before being placed on therapy. The control group was composed of consecutive unselected cases treated at this hospital, by the Cardiology Division, prior to the use of anticoagulants for acute myocardial infarction, (1940 to 1946). In other words, patients in the control group were not cases discarded from the anticoagulant group; they were not selected in any way. The controls were divided into "single infarct" and "recurrent infarct" groups to correspond to the anticoagulant-treated classification. The control cases received the same general medical supervision as the treated group. Both control and anticoagulant cases enjoyed the same degree of physical activity and did not differ in occupation, economic status, or any other important characteristics.

In most instances, Dicumarol was employed although a few cases received phenylindanedione, which we consider a less desirable drug for long-term therapy. Except for a few cases where the individual's reaction to anticoagulants had been determined in a previous course of therapy, the patients were placed in the hospital for induction of therapeutic hypoprothrombinemia. This procedure is considered highly desirable, since daily prothrombin determinations are necessary at the onset owing to the varying and unpredictable responses to

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he drug. In a group of patients on the same anticoagulant, it is not unusual to find a 300 to 400 per cent variation in maintenance dosage. In general, an attempt was made to maintain cases in both groups at from 31 to 50 per cent of prothrombin activity (22 to 27 sec. prothrombin time with a normal of 14 sec.). The Quick method was used; it is considered a satisfactory clinical tool for regulation of dosage if its limitations in relation to other methods of determining prothrombin activity are recognized.[4] The usually accepted criteria were employed for rejecting cases for anticoagulant therapy. They included the presence of some defect in the coagulation mechanism; certain lesions of the gastrointestional tract, urinary tract, or central nervous system that were considered a potential bleeding point; or some functional inadequacy such as mental deficiency, emotional instability, or alcoholism. It was also necessary to exclude those patients who were unwilling to have regular tests of their prothrombin time. In each instance, care was taken by the physician to make certain that the patient and members of his family understood their responsibility and the risks involved.

After the initial induction period on the anticoagulant, blood samples were drawn from the patients in the clinic at intervals, depending upon the stability of the prothrombin time. In no case did we intentionally allow more than 2 weeks between prothrombin determinations. The patients were instructed to call the clinic later in the day of the test, or at least by the following day, for instructions as to future dosage. A team especially trained in anticoagulant therapy supervised the entire procedure.

Group with Single Infarct

This group consisted of 186 control cases and 71 treated cases. Figure 1 compares the death rate of the treated and control groups with mortality determinations made at 6-month intervals for the first 2 years, and then at yearly intervals up to 5 years. The mortality rate of the treated group is well below that of the control group except at 36 months, where it is higher by 1 case.

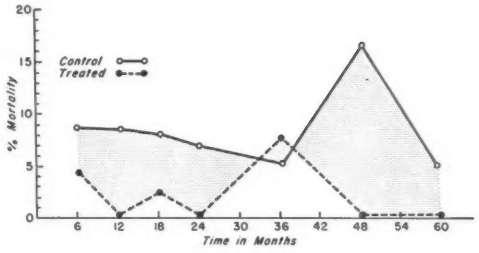

Fig. 1. Comparative mortality rates in group with single infarct.

In any group some patients die and others are lost to follow-up during the period of the study. In order to be more than fair in our evaluation, patients in the control group who were lost to follow-up during a 6-month interval were considered to be living and well at the time the mean life estimates were calculated (table 1). The rate of death in this group was 3 times greater for patients without anticoagulants than with anticoagulants. It should be pointed out that a predicted survival time of 24 years is calculated on the basis of this single pathologic condition alone, and, therefore, should not be construed as indicating the patient's remaining years of life. If the upper extreme of the confidence interval for the control is compared to the lower extreme for the treated group, the rate of death is still 2 times greater without anticoagulants than with treatment.

Group with Recurrent Infarcts

This series involved 48 control cases and 50 treated cases. The marked difference in

Table 1.—*Group with Single Infarct Predicted Survival Time (Mean Life Estimate)*

Rate of Death—3 Times Greater Without Anticoagulants

	Average	Confidence Interval in Months
Control	83 mos. (7 yrs.)	72–97 80% of cases fall in this range, 10% above and below.
Anticoagulant	292 mos. (24 yrs.)	190+ 90% of cases would fall in range of 190 or above, 10% below

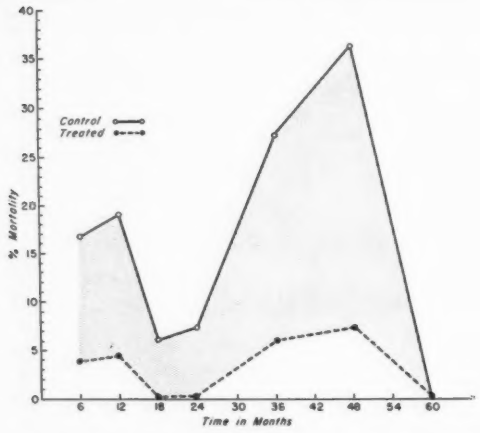

FIG. 2. Comparative mortality rates in group with recurrent infarct.

TABLE 2.—*Recurrent Infarct Group Predicted Survival Time (Mean Life Estimate)*

Rate of Death—5 Times Greater Without Anticoagulants

	Average	Confidence interval in Months
Control	39 mos. (3½ yrs.)	31–50 80% of cases fall in this range, 10% above and below.
Anticoagulant	204 mos. (17 yrs.)	132+ 90% of cases would fall in range of 132 or above, 10% below.

mortality rates during the entire period of study is noteworthy (fig. 2). Table 2 shows the predicted survival time for the recurrent group, the rate of death is 5 times greater without anticoagulants than with treatment. Again, if the upper extreme of the confidence interval for the controls is compared with the lower extreme for the treated group, the rate of death is still almost 3 times greater without treatment than with anticoagulants. The difference is most obvious in the predicted survival times of 3⅓ years without anticoagulants as compared with the time of 17 years with anticoagulant therapy.

Table 3 summarizes the total mortality rates in the 2 series at the end of each year. The most startling result is seen in the 4-year calculation

TABLE 3.—*Total Mortality Rates*

Time elapsed	Group	Control	Anti-coagulant
		%	%
1 year	Single	16.1	4.2
	Recurrent	31.2	8.0
2 years	Single	27.9	5.6
	Recurrent	39.6	8.0
3 years	Single	31.7	8.4
	Recurrent	52.1	10.0
4 years	Single	41.4	8.4
	Recurrent	62.5	12.0

TABLE 4.—*Incidence of Myocardial Infarcts (Nonfatal) during Treatment*

Duration of anticoagulant therapy when infarct occurred: 1 to 40 months

Total: 7 in 121 patients		(5.7%)
*Prothrombin time adequate	5	
Prothrombin time unsatisfactory	1	
Prothrombin time unknown	1	

* Quick 2-stage method

TABLE 5.—*Deaths*

Anticoagulant Group		
12 of 121 cases (9.9%)		
Causes		
Acute infarction	2	
"Sudden" (infarction or arrhythmia)	5	
Hemorrhage	3	
Congestive failure	1	
Hepatitis with hemorrhage	1	
Total time on anticoagulant therapy—1 to 38 months		
Control Group		
112 of 234 cases (48%)		
Extracardiac Causes: 8 cases (3%)		
Carcinoma of rectum	1	
Carcinoma of prostate	2	
Cerebrovascular accident		
1. ? Cerebral embolism, posterior myocardial infarction	1	
2. Cerebral thrombosis	2	
Unknown	2	
Cardiac Causes: 104 cases (97%)		
Myocardial insufficiency	16	(7%)
New myocardial infarction	88	(38%)

for the recurrent infarct group, where 62.5 per cent of the controls are dead versus 12 per cent of the anticoagulant-treated group. It might be well to point out again that the treated

cases represent, on the whole, more severely ill patients than do the controls.

A total of 7 new myocardial infarctions occurred in the 121 patients undergoing treatment, an incidence of 5.7 per cent (table 4). The prothrombin time was considered "adequate" in 5, unsatisfactory in 1, and unknown in 1 of them. Actually, the term "adequate time" is somewhat misleading, since the last prothrombin determination may have been taken 10 to 14 days prior to the infarction, and does not give an accurate indication of the prothrombin level at the time infarction actually occurred.

Twelve deaths occurred in the 121 treated cases. They represented 9 per cent of the total as compared with 48 per cent in the control group of 234 cases (table 5). In 2 of the deaths, in the treated group, a recurrent myocardial infarction was demonstrated electrocardiographically. In 5 others, the death was described as "sudden" and probably represented either an infarct or arrhythmia. In these 7 cases of arrhythmia or infarction, the prothrombin times were thought to be "adequate" in 5 and "inadequate" in 2. Hemorrhage was a contributing cause of death in 3 cases, although in none was the terminal event directly due to blood loss alone. Two suffered new myocardial infarctions coincident with the correction of their hypoprothrombinemia. Another patient contracted infectious hepatitis while on anticoagulant therapy, and the accompanying liver disturbance resulted in marked elevation of the prothrombin time. In this case, death was considered directly due to the hepatitis itself.

The cause of death was examined in detail in the treated group to investigate a possible relation between an inadequate prothrombin time and a coronary accident. In table 5 is an analysis of the deaths in the control group. It will be noted that deaths from other than cardiovascular causes were negligible.

Follow-up studies are of interest in patients who stopped anticoagulants after having started a long-term program. A total of 28 patients fell into this classification. Almost half were stopped because of hemorrhage, and an equal number stopped of their own accord. In addition, 2 were stopped temporarily in order to permit surgery. In 1 case, the physician believed that need for anticoagulant therapy no longer existed; in the other the physician, considered the patient no longer mentally responsible and, therefore, not suitable for further anticoagulants. Of the total number, 5 were subsequently restarted. Of the 28 patients who stopped therapy, new infarcts occurred in 14, during a period of 3 days to 20 months following the cessation. Six of these 14 infarcts were fatal. In addition, 1 patient suffered a popliteal embolus after cessation of therapy. The remaining 13 are alive 4 to 54 months after the cessation of anticoagulant therapy.

Hemorrhage

Hemorrhage has been the main reason against acceptance and wider application of anticoagulants, particularly the oral ones. Bleeding does occur and has been reported by all who use these drugs. It is an accepted, undesirable effect that we believe is less of a hazard to the patient with coronary disease than the risk from the disease itself. It is sometimes desirable to give anticoagulants to patients who present added risks, like inactive peptic ulcer or impaired liver function.

In our experience of over 5 years of long-term anticoagulant therapy, bleeding has occurred 54 times in 51 patients (42.1 per cent). What might be termed "serious" or "major" bleeding occurred in 16 cases (13.2 per cent); in 35 cases (38 instances) it could be termed minor bleeding (29 per cent). In view of the time involved, the incidence is not excessive, since the hazard from hemorrhage is considerably less than from the progress of the disease. Many of the hemorrhagic complications occurred in the early period of long-term therapy and are much less frequently encountered now. It has been under 5 per cent in the past 2 years. Very minor hemorrhagic phenomena, such as ecchymoses, epistaxes, and bleeding gums, continue to occur frequently. It is not imprudent to state that they are to be expected if the patient remains on anticoagulant therapy for any length of time. They may occur at "safe" or "inadequate" levels of hypoprothrombinemia.

TABLE 6.—*Source of Hemorrhage*

Minor—38 instances in 35 patients (29%)		*Major—16 patients (13.2%)*	
Hematuria	10	Renal	6
Ecchymosis	10	Gastrointestinal	3
Epistaxis	5	Hematomas	3
Hematomas	6	Lacerations	1
Hemoptysis	2	Mouth	1
Hemorrhoids	2	Generalized	1
Gastrointestinal	1	Retroperitoneal	1
Gums	1		
Ear	1		

Total patients—51 (42.1%)

They have never by themselves been dangerous nor have they resulted in serious trouble. Table 6 lists the chief forms of hemorrhage that have occurred in over 5 years of long-term therapy.

As previously mentioned, 3 deaths have occurred that must be ascribed to the treatment. However, bleeding was not the chief cause of death. In each instance, a new infarction occurred during the period of normal prothrombin levels following the use of whole blood and vitamin K. Autopsy examination revealed infarctions in each instance; 2 were due to thrombotic occlusion and 1 was probably secondary to prolonged coronary artery insufficiency with an inadequate hemoglobin level and red blood cell count. Should major bleeding take place, blood must be given continuously to restore the blood count and hemoglobin to normal to prevent coronary artery insufficiency, arrhythmia, pulmonary edema, and death.

For a successful program, consistently reliable prothrombin determinations are the first requisite. Without them, the practitioner should not attempt to carry out this type of therapy. Regular weekly prothrombin determinations, or semi-monthly if the patient is easily stabilized, must be done.

The management of a large number of patients on this program requires considerable time and effort, and a well-trained team is essential. Experience is required, not only for advice on dosage regulation, but in management of severe hypoprothrombinemia, both with and without hemorrhage.

DISCUSSION

We believe that the mortality figures presented here give unequivocal proof of the protective value of long-term anticoagulant therapy. Statistical analysis of our results was carried out by Dr. Benjamin Epstein, professor of Mathematics, Wayne University who suggested the method of Predicted Survival Times to demonstrate the value of anticoagulants in these patients.[5] In compiling the results, any factors that could be interpreted in more than one way were always presented against the case for anticoagulant therapy in order not to favor this form of treatment in our evaluation. An example has already been cited that, in general, the control cases included many patients with relatively mild disease, whereas our treated patients, almost without exception, were the severely ill ones. In addition, control cases lost to follow-up were considered to be living and well to the end of the period of calculation, while it is probable that many had died, either at home or in other hospitals.

Another factor should be pointed out that increases the value of long-term anticoagulant therapy in the single infarct group. The rate of death here is only 3 times greater without anticoagulants, and in the recurrent group it is 5 times greater. It must be remembered, however, that the immediate mortality (first 6 weeks) of the second myocardial infarction is in itself 30 per cent. This extra 30 per cent mortality should be added to the death rate of the single infarct group, if patients can be protected from a second myocardial infarction.

We recognize the disadvantages of this form of therapy of coronary artery disease and have referred to many of them. The facilities of a good laboratory, where many prothrombin determinations are done, preferably by the same individual, are a vital part of the program and a large factor in its success. Infrequent prothrombin determinations will not permit adequate control, and too many technicians involved in the testing will add the factor of individual variation in reaction times to the possible sources of error. The physician who directs the procedure must be entirely familiar

ith the drugs used and fully capable of coping ith any complication.

The danger of hemorrhage is constantly advanced as one of the chief objections to anticoagulant therapy, either long-term or shortrm. In prolonged treatment, minor forms of leeding occur frequently and are relatively nimportant. Since our knowledge of what onstitutes prothrombin levels adequate for rotection has increased, bleeding has been ss of a problem. Death has not been directly he result of bleeding, although hemorrhagic henomena may have eventually precipitated chain of terminal events. All of the severe emorrhagic manifestations occurred during he early stages of our work with this treatment, and we have every reason to believe their occurrence in the future will be extremely rare.

Summary

Evidence for the value of long-term anticoagulant therapy in selected cases of coronary artery disease is presented. This form of treatment has been particularly effective in the group with recurrent infarcts.

The incidence of acute myocardial infarction among patients discontinuing therapy is high; the mortality rate among those having infarcts is 44 per cent.

Hemorrhagic manifestations do not constitute a contraindication to this form of therapy.

A trained anticoagulant team, working with a well-equipped laboratory, is necessary for the success of the treatment.

Bleeding episodes are an undesirable feature that we believe is less of a hazard to the patient with coronary disease than the risk from the disease itself. In over 5 years of prolonged anticoagulant therapy, what may be termed "serious" or "major" bleeding occurred in 13 per cent of the cases, minor bleeding episodes in 42 per cent. In the last 2 years of this study the incidence has been greatly reduced, to less than 5 per cent.

Summario in Interlingua

Es presentate datos indicante le valor del uso de therapia anticoagulante a longe duration in selegite casos de morbo de arteria coronari. Iste forma de tractamento se ha monstrate specialmente efficace pro patientes con infarctos recurrente.

Inter le patientes qui discontinua le therapia il ha un alte frequentia de acute infarcimentos myocardial. Pro illes le mortalitate durante infarcto es 44 pro cento. Manifestationes hemorrhagic non es un indication contra iste forma de therapia.

Le successo del tractamento depende del disponibilitate de un ben-appunctate laboratorio e de un equipa de expertos in le dominio del anticoagulantes.

Episodios de sanguination es un eventualitate indesirabile que nos considera como minus hasardose pro le patiente con morbo coronari que le morbo mesme. In nostre experientia 5-enne con therapia anticoagulante a longe duration, sanguinationes que pote esser characterisate como "serie" o "major" occurreva in 13 pro cento del casos; episodios de sanguination minor in 42 pro cento del casos. In le curso del passate duo annos le frequentia de episodios hemorrhagic ha descendite marcatemente. Pro ille periodo illo esseva infra 5 pro cento.

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SPECIAL ARTICLE

Reassurance in the Management of Benign Hypertensive Disease

By WILLIAM GOLDRING, M.D., HERBERT CHASIS, M.D., GEORGE E. SCHREINER, M.D., AND HOMER W. SMITH, SC.D.

With the assistance of Margaret Wilson, R.N.

The therapeutic improvement achieved by administration of drugs in arterial hypertension and other disease states is widely recognized to be due to the potency of reassurance and suggestion as well as the possible pharmacologic action of the drugs employed. In this article Dr. Goldring and his associates evaluate the effectiveness of a calculated and deliberately dramatized regimen of reassurance on the blood pressure and on the symptoms in patients with benign hypertensive disease. These results help to explain why nonscientific treatment sometimes seems to be crowned with therapeutic success.—Ed.

TOO MANY investigators interested in the potential therapy of hypertensive disease, it has been evident that this therapy is complicated by the psychologic factor of reassurance. The present report is concerned with the assessment of the effectiveness of a calculated regimen of reassurance on blood pressure and subjective symptoms in patients with benign hypertensive disease. To reinforce the effectiveness of reassurance we used, as an adjunctival device, an "electron gun" that was designed to be as dramatic as possible, but without any known physiologic action other than a psychogenic one.

METHODS AND MATERIALS

The "electron gun" consisted of 3 parts: (1) a conventional, vertical Tesla coil, (2) a luminous radiator (the so-called "gun"), and (3) a standard cathode-ray oscillograph.

The Tesla coil, which was 24 inches high and 6 inches in diameter, was activated from a 15,000-volt neon sign transformer with an open type, noisy spark gap, activated by 110-volt 60-cycle alternating current. The secondary current from this transformer was further amplified by the Tesla coil to an undetermined but very high voltage so that a bluish brush-and-spark discharge radiated from the sharply pointed terminal on top. This electric discharge was clearly visible in a darkened room as a lightning-like corona several inches in radius, and was accompanied by the formation of considerable ozone. Accompanying the buzzing noise of the high-voltage discharge was the sharp, staccato noise of the spark gap.

The "electron gun" was fabricated from a conically shaped radar-tube casing 17 inches long and 8 inches in diameter at its larger end. Small blue and red lights were concealed in the smaller end of this conical tube in such a way that the light, reflected from a polished metal plate, gave the appearance of intensely high temperatures in the end of the "gun." The "gun" was attached by a single wire to the Tesla coil and superficially appeared to be activated by its brush-and-spark discharge. The "gun" was mounted on a swivel joint so that its axis could be directed toward any part of the patient's body while he sat comfortably in an arm chair.

A 4-inch cathode-ray oscillograph, activated by 110-volt 60-cycle alternating current, was placed beside the "electron gun" in a position where the screen was clearly visible to the patient. By appropriate manipulation the nurse could bring upon the screen a variety of sinusoidal waves, adjustment

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being continued until the pattern of the waves achieved a standard and preselected pattern.

Therapy with the "electron gun" was administered by a special nurse who was able to establish intimate friendship with each patient and to understand his or her difficulties. Every effort was made to obtain effective emotional transference to the nurse, and many patients became dependent on her for help in personal problems.

The patients were told that electronic devices of various types had been used successfully for the treatment of high blood pressure, and recommended that they undertake trial therapy with this particular instrument, with the assurance that it offered a high degree of potential effectiveness. No information on blood pressure was given to the patient, the nurse always replying to inquiries on this matter with assuring but ambiguous answers.

For therapy, the patient was admitted to the therapy room and seated in a slant-back upholstered chair facing the "gun." The light was then dimmed for several minutes to permit dark accommodation, during which time the nurse recorded the brachial blood pressure as determined by sphygmomanometer. On the first occasion when therapy was administered, she explained the operation of the "electron gun" in general terms, assuring the patient that though it might be frightening it was in no way dangerous. After dark accommodation had been achieved in 3 to 5 min., the "gun" was adjusted so that its "rays" were directed toward the patient's chest, and the electric current was turned on. The nurse then adjusted the cathode-ray oscillograph to a predetermined pattern.

Treatment initially lasted for only 1 to 2 min., but the period of exposure was increased on subsequent visits to 5 min.

The patients were selected from the Hypertension and Nephritis Clinic of New York University College of Medicine. All had moderately advanced hypertensive disease in the benign phase, and were selected to exclude so far as possible both the early labile phase and the accelerated phase complicated by renal or cardiac failure.

Hospitalized Patients

Nine patients received therapy during hospitalization. Table 1 records the average blood pressures obtained. During hospitalization blood pressure was recorded 3 times a day, the figures being averaged for each day. The patients were maintained in semi-ambulation and therapy was not started until the pressure had apparently become stabilized for at least 2 weeks. Thereafter, "electron gun" therapy was administered every day for 5 days a week, the blood pressure being recorded before each treatment after the patient had entered the therapy room and had rested for a few minutes in the therapy chair. During this interval lengthy interviews and periodic physical examinations were made integral parts of the study, and placebos were used in a few instances to reinforce the effects of the "electron gun." Therapy was continued until no further change in pressure was anticipated. The average pressure during therapy represents the average of all observations over a period of 1 week during which the pressure reached its apparently lowest values. The interval between beginning of therapy and attainment of these lowest pressures ranged from 1 to 5 weeks.

Table 1.—*Effect of Intensive Reassurance Therapy on Blood Pressure of Hospitalized Patients*

Patient	Control Average of 1 year in clinic prior to hospitalization	Hospitalization Average of at least 2 weeks stabilization of pressure	Intensive Therapy Average of 1 week of lowest values	Posttherapy Average of 9 to 12 mos. in clinic
	mm. Hg	mm. Hg	mm. Hg	mm. Hg
Ba	215/138	200/132	194/127	234/150
Wo	196/126	160/86	152/82	190/106
Jo	180/118	146/100	150/102	174/122
Ka	214/142	174/110	170/110	198/126
McGo	180/118	190/118	186/118	200/124
McGu	200/118	172/88	154/80	196/106
Sc	200/110	166/96	166/94	—
Si	242/132	236/112	238/118	246/144
To	200/114	162/98	164/94	200/112

After cessation of therapy all patients were returned to the clinic and examined at intervals under the same circumstances as during the pretherapy period. The posttherapy blood pressure represents the average of all observations over a period ranging from 9 to 12 months, but excluding observations within 8 weeks of the end of intensive therapy.

Out Patients

Thirty-one patients received therapy as out patients, 9 of whom had also been treated in the hospital. Table 2 records the average pressure obtained.

During therapy the patients reported twice a week to the clinic where they were examined by the same physician and then admitted to the therapy room. Multiple pressure observations were made by the nurse at each visit after a short period of rest in the therapy room.

TABLE 2.—*Effect of Intensive Reassurance Therapy on Blood Pressure of Clinic Patients*

Patient	Control Average of 1 year in clinic prior to hospitalization	Intensive Therapy Average of 4 weeks of lowest values	Posttherapy Average of 6 to 12 mos.
	mm. Hg	mm. Hg	mm. Hg
Ba	215/138	190/128	234/150
Wo	196/126	146/83	190/106
Jo	180/118	144/104	174/122
Ka	214/142	160/108	198/126
McGo	180/118	158/106	200/124
McGu	200/118	146/86	196/106
Sc	200/110	166/98	—
Si	242/132	222/114	246/144
To	200/114	146/84	200/112
Bo	205/130	190/118	240/120
Ca	226/126	200/100	206/106
Cu	200/128	182/102	200/116
DeP	180/114	156/100	180/102
Gr	196/110	162/86	208/102
Jo	196/114	180/106	218/116
Ke	186/114	166/110	—
Na	180/124	160/110	220/140
Os	198/108	178/80	216/106
Pa	190/104	174/102	180/104
Sa	188/126	140/86	188/116
Si	186/122	172/96	194/106
Su	188/110	156/88	176/96
Wa	210/124	168/100	196/106
Am	186/112	158/88	182/104
Br	188/110	184/100	—
By	184/110	169/108	—
Cr	216/122	222/126	—
Fu	190/126	140/98	174/114
Le	194/116	182/108	200/114
Ma	206/108	176/94	212/106
We	186/118	174/110	182/114

The average pressure during the month of lowest values observed during therapy was recorded. The interval between beginning of therapy and the attainment of these lowest values ranged from 1 to 9 months. Following discontinuance of therapy the patients were only observed in the clinic. The average pressure during the subsequent 6 to 12 months is also recorded.

RESULTS

In the hospitalized group, the pressure, as averaged here, was substantially lower during therapy than during the pretherapy period in 6 out of 9 patients, the average difference in these 6 patients being −39 and −28 mm. Hg in systolic and diastolic pressure, respectively (table 1). In 2 patients, the diastolic pressure decreased to below 90 mm. Hg. In all patients, however, the decrement in pressure had occurred predominantly in the last 2 weeks of stabilization in the hospital, and was apparently not related to therapy with the "electron gun." After cessation of therapy and return to outpatient status, the pressure returned to the control level in all patients, showing that the effects of hospitalization were transient.

In the outpatient group, the pressure decreased, as between the control level and period of therapy, in 15 out of 31 patients, the average decrease in these 15 patients being −36 and −27 mm. Hg in systolic and diastolic pressure respectively. In 8 of these 15 patients the diastolic pressure decreased to below 90 mm. Hg. After cessation of therapy, the average pressure during a period ranging from 6 to 12 months approached control levels. Hence it might be inferred, subject to the qualifications stated below, that intensive therapy of our patients not subject to hospitalization had reduced pressure in nearly 50 per cent of the patients, but without permanent effects, since the pressure returned to control levels after therapy was discontinued.

In view of the behavior of the hospitalized group, however, it must further be inferred that hospitalization (for a period which varied with different patients) proved as effective as intensive therapy with the "electron gun."

It is equally significant, in the general problem of the treatment of the hypertensive patient, to note that during intensive therapy all patients reported substantial subjective improvement with respect to headache, fatigue, dizziness, nervousness, and chest pain. Several patients who had been partially incapacitated were enabled to resume normal activities. The psychologic impact of intensive therapy on out patients was shown by the fact that, so long as therapy was continued, all patients reported to the clinic regularly twice a week, some for as long as 14 months, and sometimes despite the considerable inconvenience of traveling long distances and being incommoded in their daily occupations. Several of them warmly recommended the therapy to their friends.

Discussion

Four points emerge from this study. The first is the demonstration that a therapeutic regimen calculated to be dramatically impressive, but otherwise possessing no known physiologic action, can reduce blood pressure in a substantial fraction of clinic patients while maintaining ambulatory status and regular daily duties. The extent of reduction was, as might be anticipated, variable, but any discussion as to what constitutes a "significant" reduction must at the present time be based on arbitrary definition rather than physiologically reliable criteria, and the qualitative fact is the only one needing emphasis here. The success of this regimen emphasizes that reduction of blood pressure in association with any therapy, especially when the therapy is coupled with effective transference to physician and nurse, does not necessarily demonstrate a specific action.

Secondly, our observations on hospitalized patients show again, as we have previously emphasized, that the circumstance of hospitalization is effective in numerous patients, perhaps in the majority, in reducing pressure.[1] Beyond this qualitative fact, our data show that an apparently minimal pressure may be attained in some patients after 2 to 4 weeks of hospitalization, but may not be attained in others until about 12 weeks. This fact evokes caution in the interpretation of therapeutic measures instituted in hospitalized patients after only 2 or 3 weeks of hospitalization. That we failed to reduce pressure to a further extent by intensive therapy with the "electron gun" after prolonged hospitalization suggests, though it does not prove, that hospitalization alone had reduced pressure as much as was to be expected from assurance and transference alone.

Thirdly, the pressure in outpatient and hospitalized patients returned within 8 weeks or less to control levels, showing that in neither instance had anything more than a transient effect on pressure been achieved.

Lastly, in both groups, intensive therapy and reassurance again proved their effectiveness in relieving subjective symptoms and promoting psychic and physical rehabilitation: in this respect one cannot overemphasize the importance of the "enthusiastic treatment of the worried patient," to use Ayman's[2] phrase.

In order to compare blood pressure during various phases of this study it was necessary arbitrarily to select some average value over a period of 1 week or longer during which the pressure appeared to be relatively constant. However, the variability of pressure in all circumstances, including these so-called periods of stabilization, introduces an unpredictable element. In some patients during hospitalization alone, or during intensive therapy with or without hospitalization, the pressure appeared to stabilize in 3 weeks, while others required as long as 9 months. In face of this variability we cannot exclude the possibility that in some patients decreases in pressure not causally related to therapy may have occurred coincidentally with therapy. In any case, we have no reason to suspect that the observed reduction in pressure reflects any alteration in the basic and unknown process or processes underlying the hypertensive state.

The foregoing statements make no commitment with respect to the presumed prophylactic or therapeutic value of a reduction of pressure per se in essential hypertension, a thesis defended by many investigators in this field. Nor was this study designed to assess the effect of reassurance therapy on the natural history of the disease.

Summary

The effects of intensive reassurance coupled with a dramatic mechanical but physiologically innocuous device on blood pressure and subjective symptoms were evaluated in 31 patients with benign hypertensive disease.

In 6 out of 9 patients treated in the hospital, the average decrease was 39 mm. Hg in systolic and 28 mm. Hg in diastolic pressure. In 2 of these patients, the diastolic pressure was reduced to 90 mm. Hg or below. In 15 out of 31 patients treated in the clinic, the average decrease was 36 mm. Hg in systolic and 27 mm. Hg in diastolic pressure. In 8 of these, the diastolic pressure was reduced to or below 90 mm. Hg.

All patients were substantially improved in respect to subjective symptoms, some to the point of psychic and physical rehabilitation.

We cannot confidently affirm a causal relationship between reassurance and the observed decrease in pressure because of the uncertainties involved in the selection of data of reference, and because of the possibility that the observed decrease in pressure may represent a coincidental, transitory phase in the natural history of the disease. Our data do suggest, however, that intensive reassurance is effective in reducing pressure transiently in some patients, and that it is more often effective in relieving subjective symptoms.

The mechanical device employed in this study was designed to reinforce the effectiveness of reassurance and nonspecific medical care by a dramatic and mysterious form of treatment. To the best of our knowledge, it possessed no other physiologic effect, and it is not recommended for clinical application.

SUMMARIO IN INTERLINGUA

Esseva evalutate in 31 patientes con benigne morbo hypertensive le effecto exercite super le pression sanguinee e le symptomas subjective per un intense effortio a stimular le confidentia del patiente, combinate con le uso de un psychologicamente impressionante sed physiologicamente innocue procedimento mechanic.

In 6 inter 9 patientes tractate al hospital, le reduction median del pression sanguinee esseva 39 mm Hg systolic e 28 mm Hg diastolic. In 2 de iste 6 patientes le pression diastolic esseva reducite a 90 mm Hg o minus. In 15 inter 31 patientes tractate al clinica pro patientes visitante, le reduction median esseva 36 mm Hg systolic e 27 mm Hg diastolic. In 8 de iste 15 patientes le pression diastolic esseva reducite a 90 mm Hg o minus.

Omne le patientes experientiava notabil melioratione quanto a lor symptomas subjective. In certe casos iste melioration amontava al rehabilitation psychic e physic.

Nos non pote asserer de maniera categori que il habeva un relation causal inter le stimulation del confidentia del patientes e le observate reduction del pression sanguinee. Pro un tal assertion nimis grande incertitudes esseva involvite in le selection del datos de referentia. Il etiam existe le possibilitate que le observate reduction del pression sanguinee representava un transiente phase coincidente in le historia natural del morbo. Il pare, nonobstante, que nostre observationes significa que le stimulation del confidentia del patientes es efficace in effectuar un reduction transiente del pression sanguinee in certe patientes e que illo es plus generalmente efficace in effectuar un alleviation del symptomas subjective.

Le procedimento mechanic que esseva usate in iste studio habeva le function de reinfortiar le efficacia del stimulation del confidentia del patientes (e del non-specific mesuras medical). A parte le facto que le patientes videva in ille procedimento un impressionante e mysteriose forma de therapia, le procedimento per se habeva nulle effecto physiologic, e illo non es recommendate pro futur applicationes clinic.

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CLINICAL PROGRESS

Heart Failure and Lung Disease

By HANS H. HECHT, M.D.

THE multifaceted interplay of factors leading to the onset of heart failure secondary to lung disease (cor pulmonale) has made this type of heart disease of unusual interest. It is more common than previously realized. The relatively precise methods now available for assessment of both respiratory and circulatory functions permit a pathophysiologic analysis that goes beyond the purely clinical or pathologic descriptions of "cor pulmonale." It has become obvious that this term covers a number of unrelated conditions that have little in common beyond the fact that right ventricular failure occurs. It is, therefore, not surprising that a short definition of the term "cor pulmonale" meets with difficulties. In the following pages some of the concepts on the nature, diagnosis, and management of heart failure in various types of chronic pulmonary dysfunction have been summarized to provide a general orientation. For more complete information concerning the different phases of cardiorespiratory diseases, the reader is referred to several detailed reviews.[1-4] The references cited are usually of recent origin and should be consulted for earlier observations.

PHYSIOLOGIC CONSIDERATIONS

Pulmonary Hypertensive Heart Disease

It seems clear that right ventricular failure may result from simple overtaxing of the right ventricular musculature similar to that which occurs in sudden or gradual obstruction of the pulmonary artery in animal experiments.[5-8] In man, this type of right ventricular failure may properly be termed "pulmonary hypertensive heart disease." It is analogous to left ventricular failure of the heart in arterial hypertension or in aortic coarctation, with one significant difference: elevation of the mean systemic pressure to little more than twice the normal value may become critical for left ventricular function, whereas the right ventricle seems capable of tolerating well over 5 times the normal pulmonary artery or intraventricular pressures. In young individuals a rise in systolic right ventricular pressures alone from the normal of 20 mm. Hg rarely causes difficulties unless the pressure rises well above 100 mm. Hg.

The best example of pulmonary hypertensive heart disease is represented by the patient with diffuse proliferative arteritis of the lung, described earlier by Romberg[9] and by Moenckeberg,[10] a condition that deserves the term "essential pulmonary hypertension" ("pulmonary vascular obstruction syndrome," "primary pulmonary hypertension"[11-14]). The term points to the analogy of this disease of the lesser circulation to essential arterial hypertension and replaces what has in the past usually been termed "idiopathic right ventricular hypertrophy." As in arterial hypertension, vasospasm has been assumed to be at least a concomitant feature, but its true etiology is unknown. If the medial layers of the pulmonary arterial tree are involved, a persistence of a fetal type of pulmonary vasculature may be conjectured;[15, 16] the disease may then be considered to result from an anomalous persistence of a feature which in the fetus or in examples of ventricular septal defects prevents excessive flooding of the lungs. On the other

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hand, fibrous thickening of the intima and small thrombi may be considered secondary to pulmonary hypertension.

A functionally identical situation exists in pulmonary valvular stenosis where the obstruction, however, is moved from the lung periphery to the valves themselves. Failure occurs late, since the myocardium is usually intact, and appears only if the membranous obstruction is severe enough to raise systolic right ventricular pressures above 100 mm. Hg, a point of significance in the evaluation of such patients for corrective surgery.

Two additional obstructive vascular lesions result in relatively pure pulmonary hypertensive heart disease: (1) massive thrombosis of a major branch of a pulmonary artery,[17] and (2) multiple, repeated emboli to the lung,[18, 19] a pathologic condition that has been successfully reproduced in animals.[20, 21] In either case, once an acute episode of embolization has been overcome, the clinical manifestations are primarily associated with right ventricular failure, and not with lung disease, though certain deficiencies in respiratory function may precede the onset of heart failure.[19]

A massive embolus may result in a sudden intolerable overload of an unprepared (nonhypertrophic) right ventricle; though physiologic data in man are not available, it may be suspected that "acute cor pulmonale" is simply the most dramatic form of pulmonary hypertensive heart disease.

In examples of pure mitral stenosis, a situation often arises that closely resembles this form of heart disease.[22] Secondary vascular changes develop, apparently the result of long-standing pulmonary vascular congestion, high capillary and arteriolar pressure, and pericapillary and interalveolar edema. Imperceptibly, the mechanical valvular obstacle is overshadowed by a secondary obstruction of the pulmonary vascular tree, the "pulmonary hypertension with malignant sclerosis" of Parker and Weiss.[23] If this becomes excessive, the signs and symptoms then resemble those of "primary" pulmonary hypertension except for the additional presence of left atrial hypertrophy. This "secondary" pulmonary hypertension may rise to levels equal to those seen in the primary type, and cardiac work required in forcing blood through the pulmonary

TABLE 1.—*Type Cases of Heart Failure in Lung Disease, Hematologic Data and Blood Gas Analysis*

	Ht %	Hb. Gm./100 ml.	Arterial Oxygen		Arterial CO_2 content ml./100	Blood pH units	Alveolar-arterial oxygen gradient (Tension)‡ mm.
			Content ml./100	Satur. %			
Normal	45–52	15.0	18.6	92–94*	47	7.43	12
Pulm. hypertensive ht. dis.							
Essential pulmonary hypertension. K.C., 22y, ♀, (post)†	46	13.5	17.0	92	42.0	7.43	20
Advanced mitral stenosis. G.C., 32y, ♂, (post)†	46	13.3	16.3	92	33.7	7.47	27
Massive pulm. embolism. H.R., 54y, ♂, (post)†	40	12.5	15.7	94	46.1	7.46	26
Emphysema heart (with erythrocytosis). F.U., 57y, ♂, (post)†	68	19.0	15.1	59	52.1	7.50	32
Polycythemia vera (erythremia). C.D., 58y, ♀	78	22.2	27.3	92	45.5	7.40	13
Mixed forms and allied conditions							
Pulmonocardiac syndrome (kyphoscoliosis). J.V., 45y, ♀	60	16.8	14.8	66	55.0	7.39	28
Severe obesity (150 Kg.). E.B., 32y, ♂	56	16.6	18.2	82	44.5	7.38	
Pulm. Silicofibrosis with erythremia R.V., 47y, ♂	73	18.4	22.4	91	42.0	7.40	

Note: These are resting values and indicate a general trend. Examination on exercise will obviously alter blood gas data (see text).

* Value for altitude of 4800 feet above sea level (Salt Lake City).

† Post: Indicates that the diagnosis was confirmed by autopsy.

‡ Determination of alveolar-arterial oxygen tension gradient was determined at two levels of oxygenation by oxygen tension method of Riley. Most of these determinations were performed by Dr. I. Kurita and Dr. J. McClement.

TABLE 2.—*Type Cases of Heart Failure in Lung Disease, "Hemodynamic" Data*

	Arterial-venous O_2 Dif. Vol. %	Cardiac* output ml./min./M.²	Pulm. art. pressure mm. Hg	Pulm. wedge pressure mm. Hg.	Total pulm. resistance Units†	Ratio‡ TSR/TPR
ormal	4.9	2.2–4.0	25/10	8	3	5
ulm. hypertensive ht. dis.						
Essential pulm. hypertension	8.6	1.4	110/70	12	33	1
Advanced mitral stenosis	10.8	1.1	110/85	36	40	0.9
Massive pulm. embolism	5.9	2.3	105/50	10	14	1.4
mphysema heart	4.6	3.8	80/40	4	9	2
olycythemia vera	4.1	3.3	25/12	8	3	6
ixed forms, and allied conditions						
Pulmonocardiac syndrome (kyphoscoliosis)	7.4	1.7	120/70	7	37	1.2
Severe obesity	5.1	3.0	60/22	5	14	2
Silicofibrosis with erythremia	6.1	2.3	47/29	5	15	1.8

Same cases as table 1.

* Figures corrected for body surface area.

† Pulmonary resistance given in units comparable to Ohm's Law: Resistance = potential gradient (pressure)/current flow (blood flow).[132] To convert these units in dynes/cm.$^{-5}$, multiply by 80.

‡ Relative ratio of total systemic resistance to total pulmonary resistance. In normal resting subjects, left-sided resistance is usually 5 times the pulmonary resistance.

To obtain pulmonary arteriolar resistance, wedge pressure values have to be subtracted from pulmonary artery pressure values. Except in cases of mitral stenosis or severe left ventricular failure, this represents an almost negligible correction.

TABLE 3.—*Type Cases of Heart Failure in Lung Disease, Respiratory data*

	O_2 uptake* ml./min./M.²	RQ	Ventilation† l/min./M.²	Vital cap.§ % of norm.	Maximum breath.§ cap. % of norm.	Total lung§ vol. % of norm.	Resid. vol. % of norm.	Ratio resid. vol./total cap. %
Pulm. hypertensive ht. dis.								
Essential pulm. hypertension	122	0.75	4.6	99	97	102	110	22
Advanced mitral stenosis	121	0.78	7.5‡	80	90	77	72	29
Massive pulm. embolism	136	0.76	5.4	90	50	120	130	34
Emphysema heart	134	0.86	5.5	37	16	126	413	76
Polycythemia vera	143	0.86	5.2	110	104	85‖	112‖	28‖
Mixed forms, and allied conditions								
Pulmonocardiac syndrome (kyphoscoliosis)	127	0.75	4.0	21	16	54	150	65
Severe obesity	145	0.74	6.8	63	36	83	193	23
Silicofibrosis with erythremia	136	0.80	4.1	62	92	74	108	36

Same cases as table 1.

* Corrected to STPD.

† Corrected to BTPS.

‡ Hyperventilation rest—see also CO_2 data (table 1).

§ Normal values from Prediction Tables of Baldwin, Cournand, and Richardson.[1]

‖ These are average values for 5 cases reported by W. Newman et al.[92]

ircuit may be larger than that necessary to overcome the valvular obstruction.[24] Under these conditions, even in the absence of frank failure, the diastolic murmur of mitral stenosis may become difficult to elicit, or may completely disappear, perhaps because the rate of flow may fall below the critical threshold required for the production of a murmur. In the absence of characteristic auscultatory signs and with a similar symptomatology, the distinction between advanced mitral stenosis and other types of pulmonary hypertensive heart disease may become very difficult at the bedside even on repeated examination (fig. 8). Indeed only a few specific findings such as left atrial hypertrophy seen by radiologic and electrocardiographic observations may eventually point in the right direction.

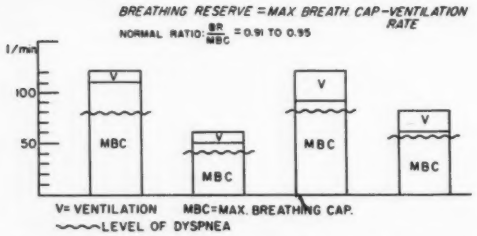


FIG. 1. This illustrates the relation of dyspnea to rate of ventilation (*V*), and to maximum breathing capacity (*MBC*). The first column represents the normal resting stage, the second illustrates an instance where dyspnea might occur with only a slight increase in ventilatory rate because of a sharp reduction in maximum breathing capacity, (example: poliomyelitis with paresis of respiratory muscles). Dyspnea as the result of an increase in the ventilatory drive together with a decrease in the maximum breathing capacity is indicated in the last 2 columns. These depict the situation in lung disease (column 3) and in heart failure (column 4). The relationships may be expressed by what has been termed the "breathing reserve."[1]

Vital capacity has often been related to dyspnea. Since most conditions that demonstrate reduction in vital capacity also show reduced maximum breathing capacity and hyperventilation, the relation, though somewhat fortuitous, holds in most instances of heart and lung disease.

For the sake of completeness, elevation of right-sided pressures as the usual consequence of left ventricular failure should be mentioned.[19] The presence of left ventricular disease as the primary cause can usually be surmised.

In pulmonary hypertension, the major pathology is found in the pulmonary vascular system at precapillary sites. It is, therefore, not surprising that, in general, no striking abnormalities in pulmonary gaseous exchange may be detected (tables 1–3). Gas exchange is not impaired though the capacity of the vascular bed to expand on exercise is diminished.[25] The oxygen extraction, i.e., the amount of oxygen in milliliters consumed per liter of air ventilated, fails to rise on exercise and it is often lower than that expected at rest. This reduction results in part, if not entirely, from hyperventilation that may have been mediated by stimulation of pulmonary nerve endings. Overactivity of the Hering-Breuer reflex (regulation of the respiratory centers by the degree of pulmonary distension) seems related to impairment of pulmonary distensibility and loss of its elastic recoil.[26-29] This ventilatory drive may become excessive, and will lead to the sensation of dyspnea if ventilation exceeds 30 per cent of the maximum possible breathing effort.[1] If the maximum breathing capacity is also diminished because of the onset of heart failure and consequent muscular fatigue, the ratio of ventilation to maximum breathing capacity may be further altered and dyspnea becomes excessive and incapacitating (fig. 1). Because of the increased rigidity of the lungs, the muscular force necessary to raise ventilation is greatly increased in subjects with various types of cor pulmonale. This increased work may be related to the early onset of dyspnea during mild exercise in these patients.[30]

Cardiac output is generally diminished and pulmonary artery pressures are excessively elevated. The wedge pressures (pulmonary end pressures) are normal (except in instances of mitral stenosis with excessive pulmonary hypertension). Consequently, the total pulmonary resistance, expressed as the mean pulmonary pressure divided by blood flow per second becomes excessively high (table 2). Because of the combination of generally reduced blood flow and increased pressure in the pulmonary circulation, conditions leading to pulmonary hypertensive heart disease show extreme values for pulmonary resistance, often exceeding those for the systemic circulation.

Arterial oxygen content and saturation are usually unimpaired or only sightly lowered, and CO_2 content is normal unless it is lowered as the consequence of hyperventilation. This is to be expected, since alveolar-capillary gas exchange is generally intact (table 1), and any tendency to oxygen desaturation of the arterial blood is obviated by the hyperventilation. Therefore, cyanosis, when it occurs, is caused by the peripheral capillary stagnation of heart failure. Polycythemia is absent.

In summary, pulmonary hypertensive heart disease is the result of right ventricular overload and with the exception of the presence of hyperventilation, the signs and symptoms are

those of heart failure. Pulmonary gaseous exchange is usually normal.

Emphysema Heart

Heart disease as the result of chronic obstructive emphysema with or without fibrosis has clinical features that are quite different from pulmonary hypertensive heart disease. It presents a complicated interplay of respiratory, hematologic, and circulatory adjustments, and shows the clinical triad of arterial desaturation, polycythemia, and evidence of pulmonary hypertension. This form of cor pulmonale in older subjects may be termed "pulmonary hypertensive heart disease with arterial oxygen desaturation and polycythemia." It deserves the more convenient label of "emphysema heart."

Arterial Oxygen Desaturation. Arterial oxygen desaturation is always present in the emphysema heart. It raises preexisting pulmonary hypertension by increasing blood flow through a restricted pulmonary vascular bed and perhaps by pulmonary arteriolar vasoconstriction, in some way similar to the hypertension of the systemic circulation that generally results from anoxia. Whatever its cause, it has been clearly established that anoxemia raises the pulmonary artery pressure in human subjects as well as in the experimental animal.[25, 31-36] In patients with emphysema a rise in mean pulmonary artery pressure also occurred when CO_2 tension of the inspired air was increased, a response that could not be elicited in normal subjects.[37] Perivascular fibrosis may further contribute to pulmonary hypertension in this syndrome by limiting the distensibility of the pulmonary vascular bed. This by itself reduces the diffusion surface of the lung particularly on exercise.[27] Pulmonary hypertension which may be present at rest, therefore, may rise sharply on exertion even without further arterial oxygen desaturation.

In contrast to pulmonary hypertensive heart disease, the emphysema heart is associated with striking changes in respiratory function. Vital capacity and maximum breathing effort are sharply diminished, ventilation is increased, a certain amount of air is trapped following deep inspiration, the total lung volume is usually augmented, and characteristically the residual lung volume, the amount of air remaining in the lungs after a maximal expiration, is strikingly increased (table 3). One may say that emphysema is present when the residual air exceeds 30 per cent of the total lung capacity.[1] The unequal ventilation of the hyperinflated lung results in lowering of alveolar oxygen tension and, in the later stages, in retention of carbon dioxide. The changes in alveolar gas concentration are reflected in the blood because the normal alveolar capillary membrane permits free gaseous interchange. The gas-blood interface, the exchange of gases from alveolar space to the arterial capillary system is not impaired until very late, and in most instances the alveolar-arterial gas gradient is only moderately increased. In the emphysema heart, elevation of arterial CO_2 content and arterial oxygen desaturation are, therefore, primarily the consequences of imperfect ventilation, which in turn is the result of deficiency in the bellows function of the chest, usually also associated with loss of pulmonary resilience. The degree of oxygen desaturation varies with the degree of impairment of chest motion and with the partial pressure of oxygen of the environment. In contrast to arterial oxygen desaturation on the basis of venous admixture (congenital heart disease, pulmonary arteriovenous aneurysms), which is independent of alveolar oxygen tension, the anoxia of the emphysema heart becomes a function of the altitude (see below). Arterial anoxia is also dependent on how much blood perfuses localized diseased areas in the lung. Ample evidence has been presented which demonstrates that blood may be shunted away from lobes made hypoxic.[38-41] This mechanism may operate in examples of extensive pulmonary fibrosis often associated with emphysema. It may represent a self correcting mechanism, the basis of which is not clear. Another factor that may counteract arterial desaturation is the presence of collateral channels between bronchial and pulmonary arteries. This may be beneficial as long as desaturated arterial blood is recirculated through ventilated areas; it is

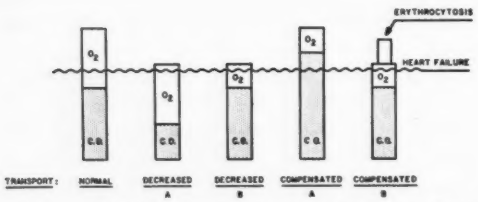


FIG. 2. *Arterial oxygen content and cardiac output ("internal oxygen transport").* Internal oxygen transport, a hypothesis relating arterial oxygen content to total blood flow delivered at the tissue site. O_2 = Oxygen content in arterial blood. CO = Cardiac output. The onset of heart failure is arbitrarily indicated by the wavy line. It should occur when cardiac output is diminished and arterial oxygen saturation is normal (*Decreased A*), or when arterial oxygenation is sharply reduced without a corresponding compensatory increase in blood flow (*Decreased B*). In normal subjects arterial desaturation causes a compensatory rise in flow (*Compensated A*) which does not occur or occurs only insufficiently in the emphysema heart (*Decreased B*). By increasing the amount of available oxygen carriers—erythrocytosis—transport can be increased (*Compensated B*). Polycythemia may be considered to represent a compensatory mechanism.

wasteful if recirculation occurs through poorly or nonaerated regions.[34] The existence of extensive collateral channels may explain the occurrence of left ventricular enlargement and even the left-sided failure occasionally observed in the emphysema heart.[42]

The hemodynamics of the emphysema heart are likewise different from pulmonary hypertensive heart disease. Cardiac output, which was low in the latter group, is usually normal or higher than normal in spite of the fact that heart failure is present.[32, 35, 43-46] Its relation to arterial desaturation has been mentioned.[36, 43] The elevation of the pulmonary artery pressure is generally of moderate degree in the resting subject and, therefore, the quotient of pressure/flow, the pulmonary resistance, is only moderately elevated or may be normal (table 2). It seems clear that the alterations in vascular pressures are usually not of sufficient magnitude to cause overtaxing of an otherwise normally functioning myocardium: they can be tolerated for decades, particularly in younger subjects, before the findings of an emphysema heart become evident.

It is quite apparent that arterial oxygen desaturation assumes a pivotal role in emphysema heart. However, arterial desaturation of a degree encountered in human subjects does not by itself cause heart failure. The supply of desaturated blood to the coronary arteries[47] will have an adverse influence in older subjects who may already have a poorly functioning myocardium, particularly if cardiac work is increased by even a moderate pulmonary obstruction, and by the hypoxia itself. It seems necessary to assume the presence of a "myocardial factor" in the emphysema heart. Except to state that degenerative heart disease of the arteriosclerotic type is likely to be present in these older subjects, no information is available that would allow a more precise definition. The myocardial component as a contributory source of heart failure in emphysema may be demonstrated if one considers that the supply of oxygen to the tissues is not only dependent on the tension of oxygen and carbon dioxide at the delivery site, but also on the total amount of oxygen delivered per unit time. This "internal oxygen transport"[35] is the product of blood flow and arterial oxygen content (fig. 2). It will be diminished if blood flow is reduced and arterial oxygen content remains normal (low output failure), or if blood flow and cardiac output remain normal but arterial oxygen content is decreased (emphysema heart). As stated, in normal subjects arterial oxygen desaturation raises cardiac output, so that the transport mechanism remains effective in the face of a low arterial oxygen content. If a "myocardial factor" such as arteriosclerotic heart disease impairs the capacity to increase cardiac output sufficiently, internal oxygen transport will become deficient and the signs of forward failure may become evident. This type of heart disease then would be another type of a low output failure. Though cardiac output is "normal" by comparison to a subject with normal arterial oxygen saturation, it is too low for a subject with arterial oxygen desaturation. This concept of emphysema heart fits several observed facts, as for example the sharp decline in renal blood flow in the face of a normal output.[35, 48]

Cyanosis. These unfortunate subjects often show intense cyanosis, and the term "black cardiacs" has been reserved for them. Cyanosis

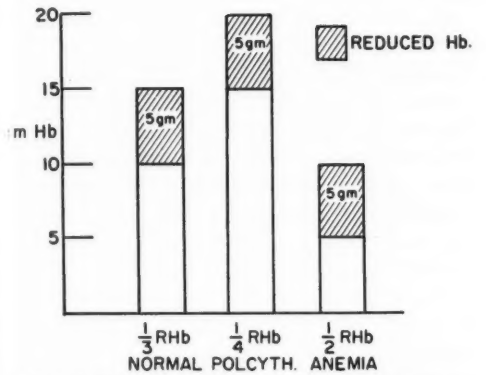


FIG. 3. *Visible cyanosis: mean capillary oxygen unsaturation of 6–7 vol. per cent or 5 Gm. reduced Hb./100 ml.* Cyanosis is primarily dependent on the amount of reduced hemoglobin circulating through the capillary bed.[49] In normal subjects approximately 3–4 vol. per cent of reduced hemoglobin is present in capillary blood, equivalent to about 3 Gm. reduced Hb./100 ml. (1 Gm. Hb. = 1.34 vol. per cent oxygen). It takes 5 Gm. of reduced Hb. in the capillary bed to cause a cyanotic appearance irrespective to the total circulating hemoglobin. In a normal subject with 15 Gm.Hb., cyanosis will not be noted unless ⅓ of the total hemoglobin is in the reduced form. In abnormal subjects cyanosis depends on the arteriovenous difference in oxygen concentration and the degree of arterial desaturation. In a polycythemic subject with a Hb of 20 Gm./100 (middle bar), only ¼ of the circulating hemoglobin must be in reduced form before cyanosis appears (5 Gm. of 20 Gm.), while an anemic subject with 10 Gm. Hb./100 ml. would not become cyanotic unless ½ of his circulating hemoglobin were in the reduced form (5 Gm. of 10 Gm.). A subject with only 5 Gm. Hb./100 ml. should never be cyanotic. The chart illustrates that the level of hemoglobin is an important determinant for the appearance of cyanosis. Other factors are listed in the text.

is dependent on an absolute amount of reduced hemoglobin present in the capillary bed,[49] (fig. 3). In heart failure, cyanosis appears, because sluggish capillary flow results in excessive unloading of oxyhemoglobin in the periphery. In the emphysema heart, in addition, as the result of arterial desaturation an abnormal amount of unoxygenated hemoglobin is present at the capillary level before utilization and unloading occurs. The two factors, one central, one peripheral, combine to make cyanosis intense. Furthermore, in a polycythemic subject, the absolute amount of reduced hemoglobin in the capillary bed (5 Gm./100) related to visible cyanosis, is exceeded at levels of arterial desaturation which in a normal subject will not cause cyanosis. The intense cyanosis of these "black cardiacs" has, therefore, a sound physiologic basis. Cyanosis, be it central or peripheral, is greatly modified by the thickness and pigmentation of the skin: it is more apparent in Mediterranean races and American Indians than in races of northern European extraction. The cyanotic appearance is, therefore, the resultant of many factors, and it cannot be used to assess degrees of arterial oxygen desaturation at the bedside.[50] It is of interest that Ayerza, who described the "black cardiacs,"[13] must have referred to the emphysema heart, but his students attributed the clinical picture to (syphilitic) pulmonary endarteritis (essential pulmonary hypertension). "Ayerza's disease" (cyanosis with pulmonary endarteritis) may really only be seen in examples of excessive pulmonary hypertension with venoarterial shunts (pulmonary hypertension associated with a patent ductus arteriosus or a septal defect).

Erythrocytosis. Arterial oxygen desaturation causes a relative and absolute increase in red cell mass: erythrocytosis ("secondary" polycythemia). This is the third of the triad that is present in heart disease associated with emphysema. This particular type of erythrocytosis usually does not appear until arterial oxygen saturation falls to 70–75 per cent of normal.[35] This polycythemia disappears when arterial saturation rises above this value as it might after surgical correction for congenital heart disease.[51, 52] It should be made clear that the threshold of "trigger value" which initiates erythropoiesis must be maintained over long time periods; an occasional higher resting value obtained in a polycythemic and emphysematous subject under treatment does not negate this relationship, since subjects who are mildly anoxic may become much further desaturated during periods of muscular work[53] or during sedation and sleep.

The exact mechanism by which this type of polycythemia is produced has not been elucidated. The concepts that arterial anoxia stimulates the bone marrow directly and that bone marrow anoxia represents the primary stimulus for erythropoiesis have been entirely conjectural. Measurements of "bone marrow

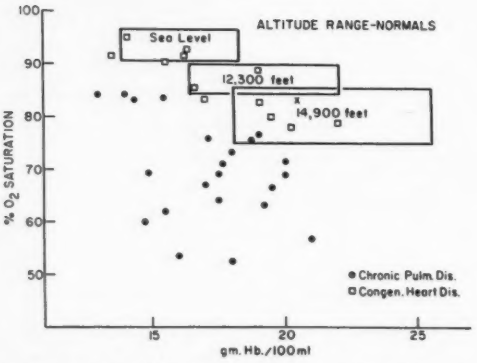


FIG. 4. *Arterial oxygen saturation and erythropoiesis.* In chronic pulmonary disease, production of hemoglobin in response to arterial desaturation is impeded when compared with the response seen in residents at high altitude reported by Hurtado.[62] A more normal response is seen in patients whose arterial desaturation is on the basis of a congenital veno-arterial shunt. *X* represents a subject with "Monge's" disease. The boxes represent the normal values for hemoglobin and arterial oxygen saturation at 3 different altitudes.[62]

oxygen tension" from blood samples obtained by sternal or iliac crest puncture may by themselves leave room for argument. Such measurements, reported in cases of polycythemia vera,[4, 54, 55] or in anemia with evidence of erythropoietic activity,[56] have not differed from normal. In polycythemic subjects with cor pulmonale or congenital heart disease, values did not differ from those of other subjects in congestive heart failure, and were usually slightly above those for mixed venous blood.[57] On the other hand, anoxia has been shown to be related to erythropoietic substances in the circulating blood ("hemopoietines").[58] Recent observations on erythropoiesis in parabiotic rats with one member made anoxic,[59] the appearance of polycythemia in litters of mice and rats whose mothers were kept in low pressure chambers,[60] and reticulocyte stimulation by plasma of anemic rabbits[58] lend support to the concept that this type of polycythemia occurs as an indirect effect of lowered arterial oxygen tension on bone marrow activity.

Erythrocytosis and heart failure occur in close association with each other, but one is apparently not the cause of the other. Heart failure obviously does not cause a relative erythrocytosis though it may, of course, result in an increase in total circulating blood volume. It is not clear whether a marked increase in red cell mass with an increase in blood viscosity may raise intravascular pressures and may constitute an additional cardiac load. Though we have seen an instance in which cardiac changes seemed related to the level of red cell mass, the infrequent occurrence of heart failure in polycythemia vera and in arteriovenous aneurysms of the lung makes it likely that such a relationship is not the usual one. On the other hand, as figure 2 shows, the increased capacity to carry oxygen in erythrocytosis, the consequence of an increased red cell mass, may be considered beneficial from a hemodynamic standpoint. However, it is rarely an effective compensatory mechanism.

In emphysema heart disease, the anoxic stimulus for erythrocytosis is opposed by a mechanism that prevents an effective rise in red cell mass, so that the polycythemia is considerably less than expected when compared to the response of normal subjects to decreased oxygen tension by altitude,[35, 62, 63] (fig. 4). It has been claimed that this blocking effect may be the result of an iron deficiency ("anemic polycythemia") or that it may be on the basis of frequent and recurrent pulmonary infections.[63] The polycythemia of chronic lung disease, however, need not necessarily be considered the equivalent to the erythrocytosis of high altitudes. Even superficially, there are important differences. The changes occurring in response to altitude are invariably accompanied by hyperventilation and are associated with low CO_2 tension and alkalosis,[64] while high CO_2 tension and low pH are the rule in emphysema. The polycythemic response to altitude appears gradual and linear,[61, 62] while in congenital venoarterial shunts as well as in chronic lung disease polycythemia, as stated, seems to require a threshold level of sustained desaturation. At any rate, the defect in emphysema involves cellular hemoglobin production since, as table 4 demonstrates, the mean corpuscular hemoglobin concentration is

ignificantly lower than normal and the polycythemic cells are often hypochromic.

In summary, the emphysema heart is associated with the triad of pulmonary hypertension, arterial desaturation, and polycythemia. None of these alone is severe enough to result in right ventricular failure, but they act in unison on a poorly functioning myocardium. Since pulmonary function is also grossly impaired, the disease involves the entire cardiorespiratory mechanism. It is possible that the "myocardial factor" is senile heart disease and that the pulmonary dysfunction merely changes the clinical manifestations of arteriosclerotic heart disease to those of the emphysema heart. The possible pathways leading to this type of heart disease are indicated in table 5.

Mixed Forms

The two types of heart failure in chronic lung disease are not always sharply separated and features of one may overlap that of the other. Severe emphysema in young individuals may show many of the features common to the simple hypertensive type, and the former may begin to resemble emphysema heart if arterial desaturation becomes evident. Recently, heart failure secondary to ineffective pumping action of the chest cage, resulting in imperfect ventilation but not associated with emphysema, has been reported in an example of amyotrophic lateral sclerosis, and in a case of extensive calcification of the pleura.[65] Similar changes may occur in extremely obese individuals,[66, 67] who may show arterial desaturation and pulmonary hypertension (see tables 1–3). Under these circumstances, changes in cardiorespiratory function occur that are similar to those seen in the emphysema heart.

In certain types of *congenital heart disease*, venoarterial shunts with severe arterial desaturation on the basis of venous admixture may be found where the right ventricle has to work against the peripheral arterial system. Again, the triad of arterial desaturation, polycythemia, and increased right ventricular pressures ("systemic right ventricle") appear. The situation is entirely analogous to the steps leading to emphysema heart. Heart failure is not frequent, however, once survival beyond the first few months of life has occurred, and very excessive degrees of desaturation and of polycythemia are tolerated for many years. This again suggests that an essential "myocardial factor" is present in the older subjects with emphysema and fibrosis.

In normal subjects, transfer of oxygen from the gaseous to the liquid phase across the alveolar capillary membrane occurs with only a slight loss of oxygen tension from the alveoli to that end of the pulmonary capillary which drains into the pulmonary venous system. This "diffusion capacity" may be impaired in various granulomatous diseases of the lung or in diffuse interstitial fibrosis producing the syndrome of "alveolar capillary block."[68] The impedance of gas transfer is rarely severe

TABLE 4.—*Mean Corpuscular Hemoglobin Concentration (MCC) in Emphysema Heart*

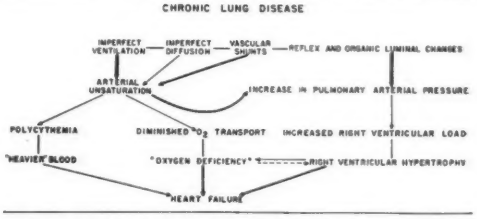
	No. of Cases	MCC (%)	S.D.	*p*
Normal				
Present series	19	32.3	1.8	—
Wilson et al.[63]	12	31.5	1.5	—
Erythremia	5	31.1	1.4	Not sign.
Emphysema heart				
Present series	23	29.5	2.1	0.03
Wilson et al.[63]	14	29.6	1.5	0.01

Similar data have been reported by Hurtado and associates.[62] Altitude polycythemia shows normal values for MCC.

S.D.—Standard deviation.

p: Probability. Values smaller than 0.05 are considered statistically significant.

TABLE 5.—*Factors of Importance in the Development of Heart Failure in Chronic Lung Disease*



The complex interrelationship of multiple factors leading to heart failure is indicated. The thickness of the arrows is somewhat proportional to the importance of the factor from which the arrow originates.

enough to cause arterial desaturation at rest, largely because of a compensatory increase in ventilation. The syndrome is characteristically associated with arterial oxygen desaturation appearing on exercise, because the increase in ventilation is now insufficient to provide the needed compensation.

Such low diffusion capacities with or without emphysema have been observed in various granulomatous lesions of the lung such as sarcoidosis,[69] acute hematogenous ("miliary") tuberculosis, chronic consolidation, scleroderma, beryllium fibrosis.[2, 3] None of these conditions is likely to result in heart failure unless fibrosis and emphysema are also present. The increase in the alveolar-arterial gradient, therefore, should not be a significant factor in the development of cor pulmonale, and heart failure in this group is usually the consequence of associated pulmonary hypertension (pulmonary hypertensive heart disease).

Kyphoscoliotic Heart Disease. Pulmonocardiac failure or kyphoscoliotic heart disease,[70, 71] is one type of cardiorespiratory involvement that respresents a clear combination of the two types of involvement. Obviously, the respiratory functions are grossly impaired because of the severe chest deformities, and ventilation is inadequate. As a consequence, arterial desaturation and polycythemia are frequently present. Somewhat surprisingly, extremely high pulmonary artery pressures, in the range of those seen in essential pulmonary hypertension, have been recorded.[71] The combination of these factors leads to early heart failure, even in young subjects, and in the face of a normally functioning myocardium. The reason for the excessive elevation of pulmonary artery pressure that we have observed in all cases of this type remains unexplained. It is quantitatively not reasonable that purely mechanical factors, which have been implicated, account for the elevation of pressures.

The relatively rare instances of heart failure following thoracoplasty seem to belong to this group.

Diagnosis

Precise measurements of hemodynamic and respiratory function have served to clarify the significance of several physical findings and have helped to quantitate some of the radiologic and electrocardiographic observations encountered in various cardiorespiratory disorders. No attempt is made in this section to give a complete discussion of the symptoms and signs of cor pulmonale in its various forms. A few observations, however, have been particularly helpful in clarifying certain interrelationships commonly encountered in heart failure and lung disease.

Clinical Diagnosis

This history of pulmonary hypertensive heart disease, particularly that due to essential pulmonary hypertension, is remarkably short. Dyspnea and fatigue are rapid in onset as one might expect if these are to a large extent the signs of an acutely failing heart. One of our patients worked full time as an operating room nurse until 3 months before death; another subject was an amateur long-distance runner until 1 month before his first hospitalization. In contrast, in emphysematous subjects, dyspnea usually precedes heart failure for years. The symptom here is linked to the pulmonary disease and the abnormality of the chest cage rather than to myocardial failure. In a polycythemic subject, the presence of dyspnea, in contrast to fatigue and lassitude, favors the diagnosis of erythrocytosis ("secondary" polycythemia). Dyspnea is not a feature of polycythemia vera (erythremia). On the other hand, patients with erythremia have a distinct set of symptoms that apparently are related to the plethora, the overfilling of the vascular bed. These subjects usually complain of headache, dizziness, roaring, a "tight" sensation, tingling and itching when vasodilation is produced, as in a warm bath.[72] These symptoms are relieved by bleeding. If these signs are present in erythrocytosis ("secondary polycythemia"), they are superimposed on dyspnea and on the other symptoms of pulmonary and cardiac disease. Bleeding in these patients may alleviate this portion of their complaints though it may not improve the cardiorespiratory symptomatology.

Chest pain as a manifestation of pulmonary hypertension is another symptom often elicited.

It has the characteristics of angina pectoris and may be relieved by nitroglycerin. It has been claimed that the pain is caused by overdistention of the pulmonary artery,[73] but there is little objective information that could not apply equally to the concept of coronary insufficiency on the basis of excessive right ventricular hypertrophy with the muscle mass outgrowing its own blood supply.[47] That the pain occurs on exercise is not surprising, since, under these conditions, a sharp increase in total pulmonary resistance associated with increased work performance occurs frequently.

The demonstration at the bedside of right ventricular hypertrophy by palpation of the precordium is usually possible, even in adults; but the expanded fixed "inspiratory" position of the chest cage in ventilatory defects commonly makes it difficult to demonstrate this component directly in the emphysema heart. Therefore, the accentuation of the second pulmonary sound assumes added significance. An accentuated, snapping second sound can be considered definite evidence of pulmonary hypertension unless right ventricular failure is present (fig. 5). By "accentuation" is implied that the second pulmonary sound (1) is much louder than the first, (2) is louder than the second sound in the aortic area, and (3) that first aortic and pulmonary sound are of about equal intensity. The sign is of value only if one can be assured that aortic and pulmonary sounds are being transmitted to the precordial areas with equal loudness. Since observations correlating this sound with intraventricular or pulmonary artery pressures are generally not based on simultaneous recordings, only a rough quantitation is possible.

Increased pulmonary artery flow into a relatively normal pulmonary vascular bed also causes accentuation of the second pulmonary sound, a characteristic finding in interatrial septal defects. Without additional laboratory information the separation of moderately increased flow from increased pressure with normal or reduced flow on the basis of clinical findings is difficult, if at all possible. Interatrial septal defects occasionally show splitting of the pulmonary second sound as well. Evidence of an increased blood flow, rather than increase in pressure but with reduced flow, may also be surmised from the fluoroscopic picture of dense lung fields with expansible pulsation of major branches of the pulmonary artery ("hilar dance").

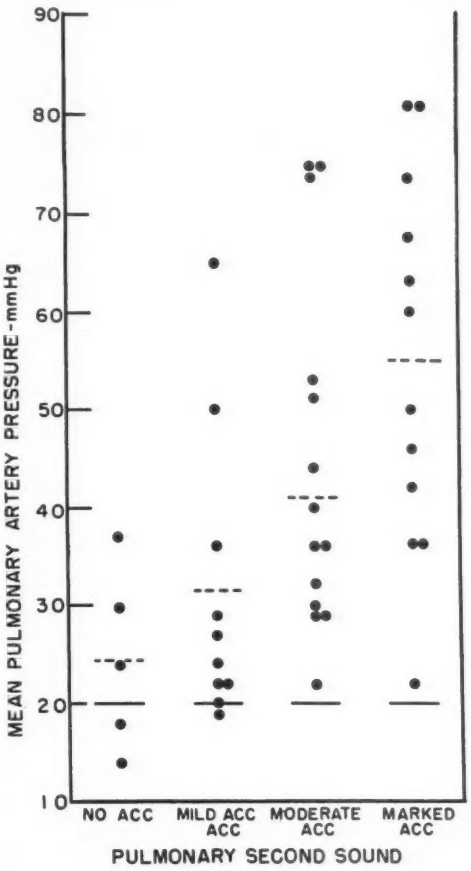


FIG. 5. Relation of pulmonary vascular pressures to an increase in intensity of the second heart sound over the pulmonary area. Relation of P_2 to mean pulmonary artery pressure in 50 subjects. Wide variations occur but a general correlation is apparent. It should be remembered that measurements were not made simultaneously, and that the presence of heart failure tends to diminish P_2. Mean values are indicated by a dashed line. In these patients, an increase in pulmonary blood flow, another cause for an increase in P_2, had been ruled out. *Acc* = Accentuated sound. (Prepared by D. Patel, M.B., B.S.)

In pulmonary hypertension, whatever the cause, loud systolic murmurs may appear

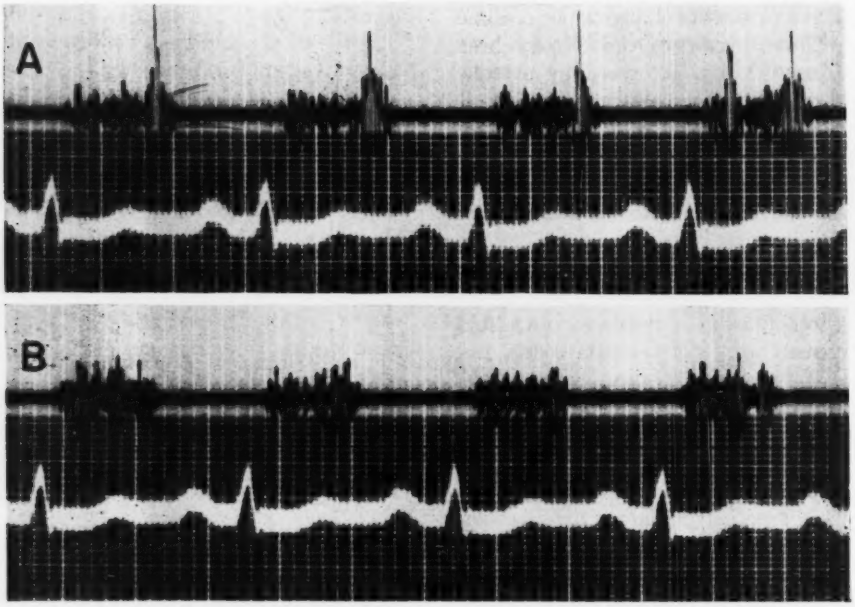


FIG. 6. Pulmonary hypertensive heart disease. Phonocardiograms of a 28-year-old veteran with obliterative pulmonary arteriolosclerosis. *A* record from pulmonary region, *B* from the apex. Note loud systolic murmur and sharply accentuated P_2. The presence of the murmur suggested at first a ventricular septal defect. When this had been excluded by cardiac catheterization, mitral insufficiency was suspected. At autopsy no cause for the murmur was found except severe concentric right ventricular hypertrophy.

along the left sternal border which may be transmitted to the apex and into the back. These may be loud enough to simulate congenital heart disease or mitral insufficiency.[12, 17] An almost unbelievable example in a patient with essential pulmonary hypertension is illustrated in figure 6. Since the findings of an incompetent tricuspid valve are absent, the significance of these murmurs has remained obscure. In addition, a dilated pulmonary valve ring may cause the high-pressure diastolic blow of pulmonary regurgitation (Graham Steell), and in some instances a semilunar opening click[74, 75] may appear as an extra sound over the pulmonary artery in early systole. It is of interest that cardiac irregularities—particularly atrial fibrillation—are quite infrequent in any type of cor pulmonale.

One feature characteristic of marked restriction of the pulmonary vascular bed and, therefore, common in various states of heart failure associated with lung disease is the occurrence of paradoxical pulsations or rather the accentuation of the normal inspiratory decrease in pulse amplitude. This may be so marked that constrictive pericarditis may be suspected.

Radiologic and Electrocardiographic Diagnosis

X-ray Diagnosis. The radiologic picture of emphysema need not be discussed. It should be remembered that in addition to the characteristic chest cage and pulmonary findings, the heart shadow in the anteroposterior view often demonstrates a lifted apex, due to right ventricular hypertrophy, and a bulging pulmonary artery, but that a completely normal cardiac shadow may be observed in the face of arterial desaturation, pulmonary hypertension, and erythrocytosis (fig. 7).[76-78]

The radiologic findings of pulmonary hypertensive heart disease and particularly of essential pulmonary hypertension have emerged as helpful and almost pathognomonic findings.

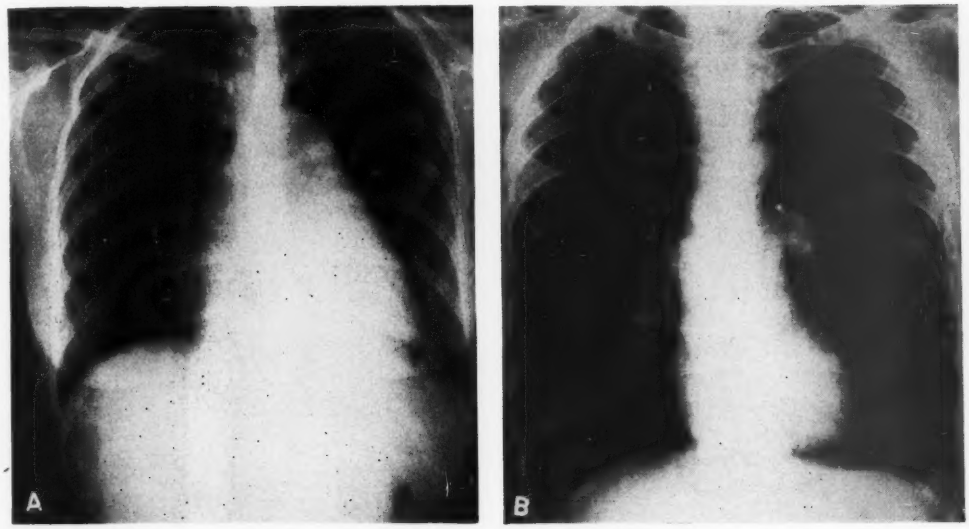


FIG. 7. X-ray configuration in cor pulmonale. *A*. Pulmonary hypertensive heart disease. K.C., age 22, an operating room nurse with essential pulmonary hypertension (see table 1) on the basis of pulmonary arteriolosclerosis (autopsy). Note diffuse cardiac enlargement, enlarged pulmonary conus, accentuated hilar markings, and decrease in vascularity of the distal segments of the lung fields. *B*. Emphysema heart. L.O'D., age 58, male salesman, with asthma and emphysema of 20 years' duration (autopsy). Note marked increase in thoracic cage, hyperaeration of lungs, small heart with lifted apex (a sign of right ventricular hypertrophy). Prominence of the pulmonary artery main stem and of the larger branches is present.

As figures 7 and 8 demonstrate, the films are characterized by (1) a normal chest cage, (2) cardiac enlargement, often of an unusual degree, (3) heavy central hilar vascular shadows with an accentuated pulmonary conus, (4) a striking decrease in vascularity of the distal pulmonary fields, and (5) absence of left atrial distention. Essential pulmonary hypertension can be differentiated radiologically from the pulmonary hypertensive heart disease secondary to massive unilateral emboli or thrombosis in situ because, in the latter, decrease of vascularity and accentuation of the central vessels are confined to one lobe or one lung in posteroanterior films or during angiocardiography.[17] Massive unilateral embolism often demonstrates distention and pulsation of the vessels leading to the involved lobe, occasionally resulting in a localized or unilateral "hilar dance."

Electrocardiographic Diagnosis. In pulmonary hypertensive heart disease the electrocardiogram usually shows the classical evidence of right ventricular hypertrophy. In the emphysema heart, more commonly right bundle-branch block, complete or incomplete, or less well defined stages of conduction disturbances of the right ventricle may be present. The relation between predominant right ventricular hypertrophy, with the characteristic tall R waves over the right ventricle, to that of complete right bundle-branch block has been described as one of concentric hypertrophy versus dilatation. This applied to instances of sudden overloading, as in acute pulmonary embolism where disturbances in right ventricular conduction are frequent, as well as to those in whom chronic right ventricular dilatation is present to an excessive degree.[79-81] In pulmonary hypertensive heart disease with a firm hypertrophic myocardium the tall R wave pattern characteristic of an anterior rotation of the QRS loop in the horizontal plane is more common. Rotation occurring only in the frontal plane (right axis deviation without changes in precordial leads), often simply the result of cardiac rotation around the longitudinal axis,

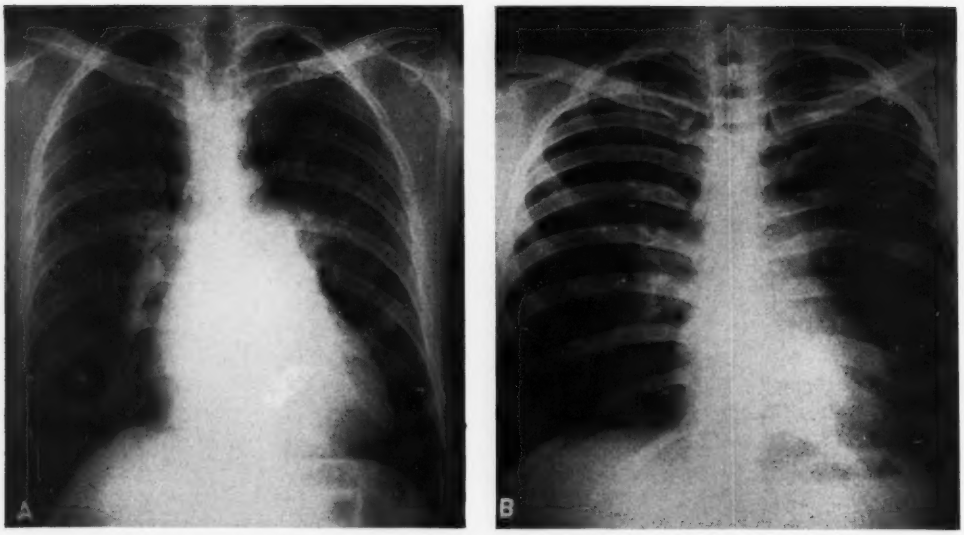


FIG. 8. Pulmonary hypertensive heart disease (special forms). *A*. R.N., age 36, male farmer with pure mitral stenosis and excessive pulmonary hypertension (74 mm. Hg mean at rest). Note similarity in cardiac configuration to figure 7*A*, but relatively normal vascular markings. Good results following commissurotomy. *B*. J.D., age 28, male veteran with multiple pulmonary embolism. Note sparsity of pulmonary vascular markings, particularly on the left with unilateral decrease in hilar markings. Cardiac configuration identical to *A* and to 7*A*. Mean pulmonary artery pressures 60 mm. Hg at rest.

may still be a sign of right ventricular enlargement, but with a lesser degree of involvement of the right ventricular outflow tract. It is more likely encountered in mitral valve disease or in the emphysema heart than in pure pulmonary hypertension because in these conditions a certain degree of left ventricular hypertrophy often coexists. "Incomplete right bundle-branch block," on the other hand, seems to occur in instances of delayed activation caused by hypertrophy of the right ventricular conus region and the upper portion of the ventricular septum, which is even normally the latest portion of ventricular musculature to undergo excitation.

In the emphysema heart in particular, right-sided precordial leads often show a qR pattern, a Q wave followed by a late R. It has been pointed out that these changes might be caused by an unusual position of the heart allowing the effects of the upper portion of the septum, including what has been termed the "crista supraventricularis" to be recorded from the precordium.[82] In changes of this type, the right atrium was usually dilated and the right ventricle assumed a more diaphragmatic position. In many instances of cor pulmonale, leads from the ensiform process (V_e) are often helpful in proving the presence of right ventricular hypertrophy.

The electrocardiographic evidence of predominant right ventricular hypertrophy is complex but a reasonably clear correlation exists between electrocardiograms of normal QRS configuration, "right axis deviation" only, "incomplete right bundle-branch block," and classical right ventricular hypertrophy, on the one hand, and progressive increase in pulmonary arteriolar resistance and increase in the external work performed by the right ventricle, on the other. In man, this correlation between evidence of right ventricular hypertrophy by electrocardiography and pulmonary artery pressures was first established in Cournand's laboratory,[83] has since been confirmed,[84] and may be seen in figure 9.

In the emphysema heart, other combinations of electrocardiographic findings often occur that are almost pathognomonic for this condition. In addition to the signs of right ventricular hypertrophy and its variants described above, positional changes of the heart,

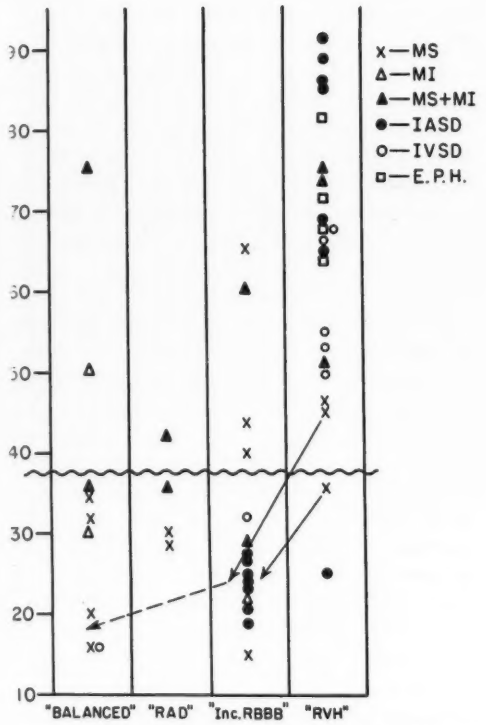


FIG. 9. The general relationship of the form of ventricular excitation (abscissa) to mean pulmonary artery pressure, mm. Hg (ordinate) at rest in 50 subjects. Characteristic right ventricular hypertrophy (*RVH*) with rightward deviation of the largest QRS axis on the frontal plane and anterior rotation in the horizontal plane (tall R over anterior precordial leads) requires a mean PA pressure at rest of 45 mm. Hg or more. One instance of mitral stenosis (*x*) with somewhat lower pressures showed low output as well, so that pulmonary resistance was markedly elevated. Following surgery, pulmonary artery pressures fell further and the ECG changed to one of incomplete right bundle-branch block (arrow). The same change occurred in the subject whose arrow finally ends up in the normal pressure range. This patient's ECG changed from *RVH* through all subsequent stages and finally was well within normal range.

Inc. RBBB refers to the RSR pattern in anterior precordial leads. There seem to be separate groups: those in whom pressures are elevated (mostly above the wavy line) and those in whom right ventricular flow is excessive but pressures remained slightly elevated or normal (intra-atrial septal defects). In some subjects this may be a normal variant. (Prepared by D. Patel, M.B., B.S.)

RAD refers to instances of rotation on the frontal plane only with slight downward displacement of the horizontal main QRS vector. This may be considered an indication of right ventricular enlargement of moderate degree, or right ventricular hypertrophy complicated by associated left ventricular enlargement. In many instances, this may be caused simply by rotation of the heart on its logitudinal axis ("vertical" position).

The "balanced" pattern may of course be a normal electrocardiogram. When associated with high pulmonary artery pressures it indicates associated left ventricular enlargement.

The wavy line arbitrarily divides considerable and marked elevation of PA pressures from normal or slightly elevated pressures. It is thought that slight elevation of pressures might not be associated with electrocardiographic changes.

MS—mitral stenosis, *MI*—mitral insufficiency, *IASD*—intra-atrial septal defects, *IVSD*—intraventricular septal defects, *EPH*—essential pulmonary hypertension.

secondary to the chest deformity, result in the appearance of deep S waves in all standard limb leads. This is a sign of an altered chest-heart relationship due to emphysema and is not indicative of cor pulmonale by itself.[85] This applies also to the appearance of unusually large but not widened P waves in V_F and in leads II and III ("P pulmonale"). Though their significance is not quite evident, they are not a sign of right atrial hypertrophy, since they may regress to normal on digitalis therapy.[86]

The spatial angle of the mean axis of QRS and of T, a fairly fixed value of the normal electrocardiogram, is not altered in many instances of predominant right ventricular hypertrophy. When the angle increases, an abnormal ventricular gradient results and inverted T waves appear in the precordial electrocardiogram in those leads that demonstrate largely upright QRS complexes. These changes are evidence of an abnormal ventricular recovery process and imply that the musculature has outgrown its own blood supply ("ventricular strain").

Differential Diagnosis of "Polycythemia"

When heart failure is present, dyspnea striking, and pulmonary disease evident, the diagnosis of "secondary" polycythemia (erythrocytosis) is not difficult. This may not always be obvious; the expiratory chest position and the use of auxiliary muscles of respiration may have escaped attention or one may find excessive polycythemia in a patient

that obviously has only mild pulmonary fibrosis or emphysema. As was stated before, the diagnosis of erythrocytosis as the consequence of lung disease requires, above all, arterial oxygen desaturation of an advanced degree generally associated with cyanosis. Lung disease and pulmonary hypertension are invariably present unless one deals with obvious venous admixture caused by venoarterial shunts. Because the level of desaturation of arterial blood is approximately the same for the stimulus of erythropoiesis as it is for the onset of heart failure, these two frequently occur together and one can safely assume that "cor pulmonale" is present when erythrocytosis is found in a patient with chronic lung disease. Examination of the bone marrow may show relative hyperplasia only of the nucleated red cell series in contrast to the hyperplasia of all cell elements found in true erythremia.[87]

In "secondary" erythrocytosis, then, the diagnostic findings mentioned above are present, and, in particular, one or the other or all of the characteristic electrocardiographic abnormalities are found. In contrast, erythremia (polycythemia vera, Osler-Vaquez) represents a primary blood dyscrasia with an increase in all cellular elements ("panmyelopathy" of Dameshek[88]). Arterial oxygen saturation is normal in most instances.[89-91] The increase in red cell mass lends these patients a characteristic reddish plethoric complexion quite different from the distressed, purplish appearance of the erythrocytotic subject. Radiologic and electrocardiographic observations are normal and hemodynamic as well as respiratory functions are usually unimpaired.[92, 93] Difficulties arise because mild emphysema or pulmonary or coronary thrombosis may complicate erythremia, and leukocytosis or a palpable spleen may be seen in erythrocytotic subjects as the consequence of unrelated diseases. The presence of systemic hypertension is much more frequently associated with erythremia, and is uncommon in cor pulmonale. By the use of these various parameters it is usually, but not always, possible to arrive at the correct diagnosis. Typical examples of erythrocytosis and of erythremia and an example of erythremia with pulmonary fibrosis are given in tables 1–3. Clubbing of the fingers—a form of "pulmonary osteoarthropathy"—is not of great help, since it has been observed in erythremia and may occur as a familial disorder in the absence of lung disease or polycythemia.

Erythrocytosis with arterial desaturation, but without demonstrable pulmonary disease, of course points to a venous admixture syndrome, either on the basis of congenital defects of the heart, including reversal of flow through a patent ductus arteriosus or a septal defect, or as the result of a pulmonary arteriovenous aneurysm. In the former, the shunt is usually demonstrable by cardiac catheterization or by dye injections; in the latter, characteristic pulsatile shadows may be seen in the lung fields radiologically in the absence of cardiac hypertrophy, electrocardiographic anomalies, elevated pulmonary vascular pressures, or abnormal catheterization data. Dye curves may also be normal. Occasionally the tell-tale x-ray findings may be absent, and under these circumstances the diagnosis has to be made by exclusion.

Monge's disease (chronic mountain sickness) has to be considered in the differential diagnosis of arterial desaturation in certain areas.[94] It has not been described in the United States, but one patient from Climax, Colorado has been examined by us and demonstrated evidence of chronic nonemphysematous pulmonary disease, apparently too mild to be of consequence at sea level. The "emphysematous types" of chronic mountain sickness described by Monge appear to be simply instances of the emphysema heart.[95]

Management

The logical management of cor pulmonale must be concerned with the many interrelated pathophysiologic factors that have been discussed in an attempt to break a chain of events such as has been outlined in table 5. The management is essentially palliative, since the ultimate causes for emphysema and for pulmonary hypertension are unknown, and the treatment of such factors as heart failure, arterial oxygen desaturation, and polycythemia are supportive and temporary. Nevertheless,

certain polypragmatism is indicated and ppears to be effective generally.

Heart Failure in Cor Pulmonale

The treatment of heart failure in cor pulnonale and its subgroups differs in no way rom other types of heart disease.[3, 96] The tatement that digitalis is less effective than in ther types of low-output syndrome may have een based on the misinterpretation of dyspnea. Many patients receive digitalis for decades because of this symptom of pulmonary disease and obviouly are not relieved by it. Digitalis, diuresis, and low-sodium intake are effective in failure of cor pulmonale,[96-98] though larger doses than usual are occasionally needed.[97] The immediate effect of digitalization in these subjects may be a further rise in pulmonary artery pressure as the result of increased myocardial function. Eventually, pulmonary artery pressures and cardiac output decrease as full compensation is restored and arterial oxygenation improves.[3, 96] The choice of the digitalis preparation seems immaterial, and the claim that strophanthus glycosides are superior in any type of cor pulmonale has not been substantiated.

Pulmonary Disease

The treatment of "chronic lung disease" and the correction of the abnormal mechanics of respiration is approached in two ways. First, pulmonary and bronchial infection and bronchospasm are frequent and often sustained either as the result of or, at least in part, as an etiologic factor in the ventilatory defect. The infection should be treated with vigor, since thereby one of the frequent precipitating causes of heart failure may be removed.[99, 100] By opening narrowed and inspissated airways, alveolar ventilation is improved, and, in consequence, arterial oxygen saturation rises, pulmonary artery pressure falls, and CO_2 retention decreases.[3, 96, 97, 100, 101] This may be so effective that the stimulus for erythropoiesis is withdrawn and the erythrocytosis of anoxia may disappear. Thus it is possible by the judicious use of antibiotics, parenteral or rectal theophylline, by oral administration of expectorants and bronchodilators, and particularly by aerosol inhalation of various epinephrine congeners,[102, 103] detergents, or trypsin[104,105] to reverse the course of the syndrome. The use of adrenal steroids or adrenocorticotrophin has been suggested,[69, 106] and may be based on a reduction of certain phases of the inflammatory response. The need for such therapy seems less well established, and the possibility of accelerating preexisting fibrosis by cortisone must be kept in mind.[69] Postural drainage, advocated in young subjects with bronchiectasis and emphysema, is rarely feasible in patients with emphysema heart, but intermittent periods of positive-pressure breathing with air, oxygen, or oxygen-helium mixtures (80 per cent helium, 20 per cent oxygen) may be effective in improving alveolar ventilation.[106-108] Respiratory irritants, such as house dust, smoke, odors, and rapid temperature changes, should be avoided. Various types of city "smogs" are poorly tolerated.[101]

A second approach in the management of some forms of pulmonary disease leading to heart failure consists in an attempt to influence directly the abnormal mechanics of breathing. This may be accomplished by regular breathing exercises[109-111] or, at least, by elevation of the foot of the bed.[112] The benefits claimed for various abdominal belts, or for pneumoperitoneum, designed to place the diaphragm in a more advantageous position for ventilatory work, have remained of questionable value.[114, 115] As a desperate measure, mechanical tank respirators have been used in an effort to ventilate the lungs.[115, 116] This is obviously impractical except as an emergency procedure.

Oxygen, Carbon Dioxide, and Respiratory Acidosis

Anoxia may be so severe that there may not be time to wait for the gradual improvement in alveolar ventilation, or the mechanical difficulties are so pronounced that the measures outlined may not be fully effective. It is then necessary to improve oxygenation by more direct means. Administration of oxygen at tensions above those of the environment usually corrects arterial desaturation, even in the face of a moderate diffusion defect or of some

TABLE 6.—*Carbon Dioxide Narcosis, L.A., Male, Emphysema Heart, Age 51*

Date	Arterial Oxygen		Tension mm.	Arterial pH at 37°	Arterial CO_2		Clinical status and therapy
	Content vol. %	Sat. %			Content vol. %	Tension mm.	
Normal	19.5	96	100	7.42	48	40	
5–10–55	9.1	52	28	7.35	72.2	54	Lapses into coma and delirium on oxygen therapy, antibiotics, aminophyllin, digitalis, etc.
5–11–55	11.3	65	42	7.23	68.0	66	No improvement on positive pressure-breathing, Diamox, intermittent oxygen; still disoriented
5–16–55	10.8	59	35	7.36	61.5	51	Mentally clear; gradually improved on vigorous antibiotic therapy, bronchodilators
5–23–55	15.4	84	55	7.40	44.9	43	Discharged

This patient was admitted after having been treated with repeated venae sections and oxygen. He received continuous oxygen by mask during 100-mile trip by ambulance and arrived hyperventilating and responsive. As the excitement of the transport abated, he became delirious and appeared moribund (5–10–55). Note that as acidosis increased, CO_2 tension rose, though CO_2 content fell slightly (5–11). Improvement occurred gradually, presumably as the result of intensive therapy with digitalis, antibiotics, and bronchodilators. Neither Diamox nor positive pressure breathing seemed to be particularly effective. On 6–1–55, pulmonary function studies revealed a ratio of residual volume to total capacity of 64 per cent, a large physiologic dead space, alveolar-arterial gradient of 17 mm.

venous admixture through capillary bypasses. Oxygen administration is effective in several ways: in addition to the rise in oxyhemoglobin, the oxygen content of the plasma may be raised and pulmonary artery pressure may decline, often appreciably, and without a significant concomitant fall in cardiac output. This improvement may occur even in apparently "fixed" pulmonary hypertension of long standing.[35, 117]

Carbon dioxide elimination is not aided by oxygen administration. In fact, it has been pointed out that many subjects with arterial oxygen desaturation and elevated blood carbon dioxide levels are dependent for their respiratory drive on the anoxic stimulus of the chemoreceptors in the aortic and carotid bodies rather than on the blood CO_2 level. If anoxemia is even partially corrected by oxygen therapy, respirations might decrease for lack of a stimulatory drive, and, in consequence, CO_2 content may rise further to levels that induce excitement, drowsiness, or loss of consciousness.[3, 63, 118-120] Hypoventilation and CO_2 narcosis leading to uncompensated respiratory acidosis can also be induced by oversedation, and opiates should, therefore, be used with great reservations. The resulting respiratory acidosis raises CO_2 tension for a given content, so that a high CO_2 content is of even greater significance when pH is low. If respiration is artificially stimulated in the face of very high CO_2 content, the pH of the blood may rise, tension may be lowered, and coma and delirium may at least temporarily be held in abeyance.[120] The interplay between some of these factors is illustrated in table 6. Carbon dioxide narcosis may be prevented by the intermittent use of lower concentration of oxygen and by low flow rates. Fear of this syndrome should not preclude the use of needed oxygen in the acutely distressed subjects.

The problem of respiratory acidosis with CO_2 retention is one that represents an additional complication in cor pulmonale and cannot be fully discussed here in all its ramifications. Recently, attempts have been made to influence plasma bicarbonate levels and CO_2 narcosis by the use of carbon anhydrase inhibitors, imposing a moderate metabolic acidosis on a preexisting respiratory acidosis[121-124] It is not clear whether carbon anhydrase inhibitors exert their effect by influencing blood gas concentration, or by a reflex stimulation of the respiratory center causing hyperventilation. The decreased responsiveness of the center to CO_2, typical of chronic lung disease, is not altered by prolonged administra-

t on of a carbon anhydrase inhibitor.[125] The usefulness of carbon anhydrase inhibitors is still not definitely established, since in most instances heart failure coexisted and the improvement seemed to occur concomitant with diuresis.

Since blood and alveolar gas tensions maintain an equilibrium, changes in altitude—by causing a change in partial pressures for oxygen in the atmosphere—will influence arterial oxygen saturation, as the example of altitude anoxia demonstrates. The peculiar S-shaped form of the oxygen dissociation curve of the blood, however, insures a normal subject a stable oxygen saturation in the face of large variations in alveolar and arterial oxygen tension. If alveolar oxygen content is lowered by imperfect ventilation, or by an increase in dead space or both, the subject may become highly sensitive to a further decrease in atmospheric oxygen tension (fig. 10). Patients with moderate arterial desaturation at sea level may do very poorly on moving to even moderate altitudes such as may prevail in the intermountain region, providing the oxygen desaturation is primarily on the basis of altered alveolar ventilation and is not the result of venous admixture. For the same reason subjects with emphysema heart residing in these areas may show a remarkable improvement in their symptoms, a rise in arterial oxygen saturation, and a disappearance of their erythrocytosis upon a sojourn to sea level. It is tempting to assume that a similar mechanism—the combination of moderate pulmonary disease not readily detectable and asymptomatic at sea level, plus altitude—may be involved in chronic mountain sickness (Monge's disease).

Recent suggestions that massive doses of salicylates might restore the reduced sensitivity of respiratory center to CO_2, and may thereby be used therapeutically to reduce the hypercapnia of emphysema,[126-128] are viewed with some concern. The effects of salicylism are produced only at high plasma salicylate levels. In addition to the toxic metabolic effects and psychoses, may have a direct myocardial stimulating effect and, furthermore, may cause a sharp increase in circulating plasma volume: total circulating CO_2 transport

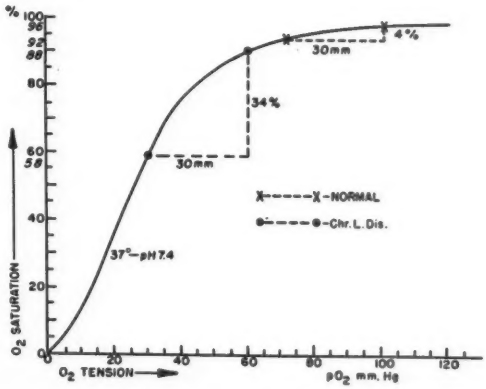


FIG. 10. The influence of altitude on arterial oxygen saturation in patients with emphysema. A subject with imperfect pulmonary ventilation has an arterial saturation of 88 per cent at sea level. This causes no symptoms, no cyanosis, and no polycythemia. He moves to an altitude which results in a 30-mm. fall in alveolar O_2 tension (5000 feet). Due to the steep slope of the oxygen dissociation curve, arterial saturation will sharply decrease (to 58 per cent), cyanosis will be definite, and in time polycythemia will appear. His normal companion with an arterial oxygen saturation of 96 per cent at sea level will decline only 4 per cent (to 92 per cent) in response to the same decrease in alveolar oxygen tension because he moves only over the flat portion of the curve. The peculiar form of the oxygen dissociation curve can serve a therapeutic purpose in subjects with emphysema living at moderate altitudes (see text). The curve is given for 37° and a blood pH of 7.4.

is therefore not necessarily lowered and congestive heart failure may be precipitated.[129]

Improving arterial oxygen content by whatever means may cause disappearance of erythrocytosis. It was pointed out that polycythemia may be looked upon as a compensatory event and its removal (by bleeding or otherwise) in the face of unchanged arterial oxygen content may precipitate heart failure because of a further reduction in oxygen supply (fig. 2). Usually bleeding does not by itself improve oxygenation, does not alter carbon dioxide retention, nor does it lower pulmonary artery pressures.[93] Therefore, from the standpoint of cardiorespiratory function, bleeding an erythrocytotic subject has little to recommend (fig. 11).[93, 130] Temporary subjective improvement, however, is occasionally

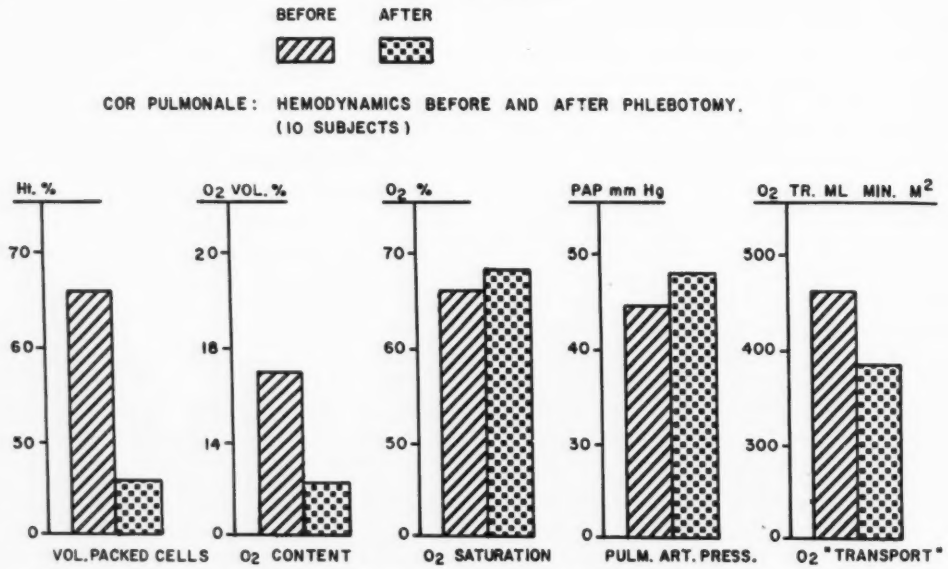


FIG. 11. Cor pulmonale, hemodynamic response to repeated bleeding. In spite of a sharp reduction in the volume of packed red cells and in oxygen content in this series, there were no striking changes in pulmonary artery pressure or in oxygen saturation following several phlebotomies. Internal oxygen transport decreased. In a patient who has received maximum benefit from other therapeutic measures, phlebotomies seem to be of little additional benefit.

noted because the symptoms of plethora mentioned above may be relieved. Furthermore, the fluidity of the blood decreases in a nonlinear fashion as the volume of packed red cells/100 ml. increases. Its reciprocal, viscosity, the force required to produce a unit rate of shear, is a function of the physical properties of the fluid, and in a non-Newtonian fluid, such as blood, varies with flow rates (level of cardiac output) and with the size of the vessels.[131] Measurements of viscosity are usually based on artificial systems comparing steady flow of the test fluid through rigid tubes of constant diameter with the flow of water. Few measurements were made in living systems and in consequence there is little information on "viscosity" of blood in the intact organism at rest, on exercise, and in various parts of the vascular system. All one can say is that it seems reasonable to assume that viscosity in larger vessels rises with an increase in the volume of packed red cells, and that its effects should be greater in patients with congestive heart failure than in normal subjects.[35] At hematocrit levels above 60–65 per cent in patients with decompensated cor pulmonale, blood stagnation with thrombus formation may, therefore, occur, and for this reason only correction of an excessive erythrocytosis seems reasonable. A complete correction to normal levels of packed red cells, however, is neither necessary nor desirable.

Treatment of Pulmonary Hypertension

The procedures outlined in the preceding section may lower pulmonary artery pressure if this was related to arterial desaturation and to carbon dioxide retention. In pulmonary hypertensive heart disease, no obvious impairment in respiratory function is present, arterial oxygenation is not severely impaired, and none of the measures outlined are effective. It is obvious that little can be accomplished if organic luminal obstruction is advanced; treatment of this phase of cor pulmonale has been least effective. In consequence, in pulmonary hypertensive heart disease the treatment of heart failure has been almost the only

form of management available with the exception of mitral valve surgery in the "secondary" type. A recent report has pointed to the efficacy of Priscoline in reducing pressure in the pulmonary vascular obstruction syndrome.[12] A few observations on the use of ganglionic-blocking agents in lowering elevated pulmonary arteriolar pressures have appeared,[132-134] though these seem ineffective in changing normal or slightly elevated pressures. Preliminary observations in our laboratory have tended to confirm these pressure-lowering effects of Priscoline in almost any type of hypertension of the lesser circulation in the face of a regularly increased cardiac output. There is, as yet, no information whether these pharmacologic responses can be translated into lasting therapeutic effects, but it is of note that the changes were associated with considerable subjective improvement which could be sustained by prolonged oral administration of Priscoline (50 mg. 4 or 5 times daily). Still, the outlook, particularly in essential pulmonary hypertension, is grave: perhaps because patients with these disorders do not seek medical attention until they have entered the final episode of their disease.

Summary

The confusing and complex interplay of factors leading to "cor pulmonale" may be somewhat clarified if the effects of excessive pulmonary hypertension causing right heart overloading ("pulmonary hypertensive heart disease") are separated from the ventilatory defects that result in arterial desaturation, erythrocytosis, and moderate pulmonary hypertension ("emphysema heart"). In the former group, heart failure dominates the clinical picture; in the latter, it is assumed that heart failure occurs on the basis of a "myocardial factor"—presumably arteriosclerotic heart disease—whose manifestations are colored and modified by the coexisting and contributing respiratory dysfunction. Overlapping of these two distinct forms occurs frequently, and pulmonary hypertension may be severe enough to be the chief precipitating cause of failure in emphysema, particularly in young subjects and in patients with kyphoscoliosis. Respiratory disturbances, fibrosis, and loss of pulmonary elasticity may accompany heart failure secondary to right ventricular overloading which may ultimately lead to significant arterial desaturation at rest and the development of polycythemia, even in this group. It is typical, however, that the disturbances leading to cor pulmonale rarely, if ever, involve the actual pulmonary function of alveolar-capillary gas exchange; they are confined to the abnormalities of the precapillary pulmonary vasculature and to the mechanical apparatus of the chest cage and of the pulmonary parenchyma concerned with breathing mechanisms.

Pulmonary hypertensive heart disease, whatever its cause, has a monotonous symptomatology that is dominated by the signs of heart failure. In cor pulmonale due to emphysema and its allied types, the clinical picture is varied, and oxygen deficiency with arterial desaturation is of central significance. It raises pulmonary artery pressure by a mechanism not fully understood, and it stimulates erythropoiesis. When erythrocytosis has occurred, heart failure from cor pulmonale will soon make its appearance. Unless the arterial oxygen content falls sharply on exercise, resting oxygen saturation values in excess of 80 per cent do not cause this type of polycythemia; nor does polycythemia as such, as in erythremia ("vera"), result in significant arterial desaturation, pulmonary hypertension, or heart failure. However, little is known concerning the hemodynamic load imposed by an increase in blood viscosity.

The management of cor pulmonale must recognize the multiplicity of factors that are concerned and should weigh their relative significance in any given subject. The kaleidoscopic appearance of cor pulmonale requires flexibility of therapy based on a grasp of the individual pathophysiologic interrelations, which may differ from patient to patient.

Summario in Interlingua

Le confuse e complexe interaction de factores que resulta in le eventuation de "corde pulmonal" deveni un pauco plus clar si on separa (1) le effectos del excessive hypertension pul-

monar que causa un supercarga del corde dextere ("morbo cardiac pulmono-hypertensive") ab (2) le defectos ventilatori que resulta in dissaturation arterial, erythrocytosis, e moderate hypertension pulmonar ("corde a emphysema"). In le prime de iste situationes, disfallimento cardiac es le dominante aspecto clinic; in le secunde le disfallimento cardiac pare occurrer super le base de un factor myocardial (probabilemente morbo cardiac arteriosclerotic) con manifestationes que es colorate e modificate per le coexistentia contribuente de dysfunctionamento respiratori. Le delimitation mutual de iste duo distincte formas es frequentemente pauco definite, e hypertension pulmonar pote esser satis sever pro ager como le principal causa precipitante de disfallimento in emphysema, specialmente in juvene individuos e in patientes con cyphoscoliosis. Disturbationes respiratori, fibrosis, e perdita de elasticitate pulmonar pote accompaniar le disfallimento cardiac como phenomenos secundari a supercargas dextero-ventricular que resulta a vices in le curso del tempore in significative dissaturation arterial in stato de reposo e in le disveloppamento de polycythemia. Nonobstante, il es characteristic que le disturbationes responsabile pro le disveloppamento de corde pulmonal involve rarmente (si unquam) le function pulmonar mesme del excambio alveolo-capillar de gas. Illos es restringite a anormalitates del precapillar vasculatura pulmonar e al apparato mechanic del thorace e del parenchyma pulmonar concernite con le mechanismo respiratori.

Morbo cardiac pulmono-hypertensive (de qualcunque causa) ha un symptomatologia monotone que es dominate per le signos de disfallimento cardiac. In casos de corde pulmonal debite a emphysema (e in le typos affin), le aspecto clinic es de character variabile, e deficientia de oxygeno con dissaturation arterial ha un signification central. Illo augmenta le pression pulmono-arterial per un mechanismo que es non ancora completemente clar, e in plus illo stimula le activitate erythropoietic. Si erythrocytosis ha occurrite, disfallimento cardiac ab corde pulmonal va evenir sin grande retardamento. Excepte in casos in que le contento arterial de oxygeno es marcatemente reducite per exercitios, nivellos de saturation oxygenic in reposo que amonta a plus que 80 pro cento non provoca iste typo de polycythemia; e polycythemia per se—como in erythremia ("ver")—non resulta in significative dissaturation arterial, hypertension pulmonar, o disfallimento cardiac. Tamen, nos sape pauco in re le carga hemodynamic que resulta de augmentos del viscositate sanguinee.

In planar le regime pro casos de corde pulmonal, on debe prender in consideration le multiplicitate del factores involvite e pondera lor signification relative in omne patiente individual. Le aspectos caleidoscopic de corde pulmonal require un therapia a alte grados de flexibilitate correspondente al individual interrelationes pathophysiologic que pote differer ab un patiente al altere.

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ABSTRACTS

AVITAMINOSIS

Stare, F. J.: Nutrition and Aging. J. Am. Geriatrics Soc. **3:** 767 (Oct.), 1955.

Sound nutrition in the elderly patient differs only slightly from that in the younger adult. A good plan should include fewer calories with a smaller proportion of calories contributed by fat and a larger proportion by protein. Dietary modifications may be necessitated by poor dentures, low income, inadequate cooking facilities, and poor appetite. Moderate activity contributes to the nutrition of the older person by stimulating the circulation, promoting an increased sense of well-being, encouraging an interest in food, and stimulating a sluggish appetite. The elderly obese person is advised to reduce, but this takes convincing because he has lived with his excess weight for a long time.

RINZLER

BLOOD COAGULATION

Lee, S. L., and Sanders, M.: A Disorder of Blood Coagulation in Systemic Lupus Erythematosus. J. Clin. Invest. **34:** 1814 (Dec.), 1955.

Detailed hematologic studies were performed on 13 patients with systemic lupus erythematosus. In confirmation of other reports, certain coagulation defects were found. In 7, an excess of an anticoagulant substance was found. This phenomenon was also present in a lesser extent in 5 other patients. The findings were slightly prolonged whole blood clotting time, prolonged clotting time of platelet-poor recalcified plasma; prolonged 1-stage prothrombin time; delayed thrombin generation but normal prothrombin consumption; and the presence of a substance that can delay the clotting time of normal plasma.

In only 3 of these 12 patients was hemorrhage a prominent symptom, and in only 1 could the bleeding be ascribed to the anticoagulant activity. The authors speculate on the nature of this disturbance and its possible relation to the L.E.-cell factor, but conclude that the pathogenesis of abnormal blood coagulation in systemic lupus erythematosus is unexplained.

WAIFE

CORONARY ARTERY DISEASE

Enos, W. F., Jr., Beyer, J. C., and Holmes, R. H.: Pathogenesis of Coronary Disease in American Soldiers Killed in Korea. J. A. M. A. **158:** 912 (July 16), 1955. Abstracted, Circulation **14:** 82 (July), 1956.

Wagner, A.: Clinical Implications of Recent Experimental Trends in Atherosclerosis. Quart. Bull. Northwestern Univ. M. School. **29:** 244 (Fall), 1955.

Among 1,000 persons in the age bracket 30 to 60 years, the unfavorable lipoprotein class S_f 12–20 progressively increased with increasing overweight. Among 39 subjects of both sexes in the age bracket 29 to 68 years who were studied for an average of 8 months, weight reduction favorably influenced the undesirable lipoproteins and the total cholesterol concentration, but only when they were quite abnormal initially.

While investigations to date have not resulted in any single panacea for atherosclerosis, by advancing our knowledge of some of the basic variables relating to this disease they have moved us in the direction of that objective. Perhaps the most important product

has been the new concept of reversibility. It is now clear that the physical state of the plasma has much to do with the development of intimal lesions, and thus far is capable of favorable manipulation. It seems very likely that in this rapidly advancing field, other therapeutic measures toward the same end will soon emerge with further understanding of the basic defects in atherogenesis.

BERNSTEIN

Alella, A.: Coronary Blood Flow and Hypoxia. Pflüger's Arch. ges. Physiol. **261:** 373 (Aug.), 1955.

The arterial oxygen saturation, the coronary flow, the mean aortic pressure, and the cardiac oxygen consumption are studied in 28 dogs in hypoxia. It is found that the coronary flow is increased, secondary to increase in mean aortic pressure and to arterial oxygen unsaturation. Independent of the degree of oxygen saturation, the mean aortic pressure increases coronary flow (mechanical effect), increases the oxygen consumption of the heart (metabolic effect), and decreases the tonus of the coronary arteries. Although the coronary arteries dilate and the blood flow to the heart increases secondary to hypoxia, these changes are not fully compensatory. When the arterial blood is about 50 per cent saturated, cardiac efficiency decreases (hypoxic cardiac failure).

CALABRESI

Kathke, N.: The Changes in the Branches of the Coronary Arteries in Hypertension. Beitr. path. Anat. **115:** 405 (Oct.), 1955.

In 7 cases of hypertension the cardiac muscle has been thoroughly examined with regard to changes of the intramural arteries and arterioles. The age of the subjects varied from 25 to 63; the known duration of the hypertension varied from 9 months to 9 years. There were 3 cases of essential hypertension, 3 of renal hypertension, and 1 of Cushing's disease. The weight of the heart varied from 410 to 750 Gms. Similar systematic observations were completed in 4 controls. The first demonstrable effect of hypertension on the cardiac vessels is arteriolosclerosis, independently of the duration of the disease and of arteriosclerotic changes in the major coronary arteries and branches. The arterioles of the papillary muscles of the left ventricle were not affected, except in 1 case. The extension of these changes of the intramural coronary vessels is apparent only in systemic investigation of the heart. The significance of these findings as a factor of coronary insufficiency, independent of arteriosclerotic narrowing of the extramural arteries, is stressed.

CALABRESI

Jaffe, H. L., and Master, A. M.: Lack of Correlation Between the Electrocardiographic Findings and the Clinical Course in Coronary Occlusion. J. Mt. Sinai Hosp., New York, **22:** 261 (Nov.–Dec.), 1955.

The authors strongly emphasize the disparity between the clinical picture and the electrocardiographic features in cases of myocardial infarction, not only during the acute phase but even months or years later. Because of the lack of correlation between the clinical state and the electrocardiographic appearance, they stress the point that the latter should be used only diagnostically and not prognostically. Illustrative of this view is a case report in which widespread electrocardiographic abnormalities of extreme degree were present. Nevertheless, the patient's clinical course was quite mild.

ENSELBERG

Iaverinos, C.: The Seasonal Incidence of Acute Myocardial Infarction in Egypt, in Relation to the Climate. Arch. mal. coeur **48:** 876, 1955.

In 460 cases of myocardial infarction occurring in Cairo and Alexandria from 1947 to 1953 the monthly incidence has a definite maximum in June and July, with a smaller maximum in April. The mean temperature has a maximum in June through September, when it reaches 26–28 C., and the increased incidence of infarction is attributed to increased work of the heart and to hemoconcentration, which may favor coronary thrombosis. Another factor is the high incidence of intestinal infections in summer. The relatively low incidence of infarction in May may be related to the low relative humidity at this time.

LEPESCHKIN

Boccardelli, V., and Boldrini, R.: The Hypoxia Test in Arteriosclerosis without Angina. Arch. mal. coeur **48:** 1123 (Dec.), 1955.

In 30 cases (50–64 years of age) in which arteriosclerotic heart disease could be assumed to be present on the basis of "clinical, radiologic, and electrocardiographic signs," inhalation of 7 per cent oxygen for 10 min. caused significant changes of S-T and T to appear in 40 per cent, but a similar test with 9 per cent oxygen at another time caused these changes to appear in only 20 per cent. An exercise test produced significant changes in 24 per cent of a similar group of patients.

LEPESCHKIN

Dogliotti, A. H., and Canfossi, A.: The Problem of Intercoronary Anastomoses. Arch. mal. coeur **48:** 1116 (Dec.), 1955.

Intercoronary anastomoses must be subdivided into (1) those anatomically present but functionally inadequate; (2) those that are both anatomically and functionally adequate, and (3) those that develop slowly after incomplete coronary occlusion. The high incidence of septal infarction shows that the second type of anastomoses is rare.

LEPESCHKIN

Steinberg, D., and Ostrow, B. H.: Serum Transaminase as a Measure of Myocardial Necrosis. Proc. Soc. Exper. Biol. & Med. **89:** 31 (May), 1955.

A method of assay of serum transaminase that is a modification of the method of Karmen, Wroblewski, and LaDue, is described.

The enzyme was present in all sera tested. In 20 normal adults the concentrations ranged from 10 to 35 units/ml. and was constant from day to day, unaffected by meals. Normal urine contained less than 1 unit/ml. Hemolysis of the sample caused a release of enough enzyme to increase the assay per ml. almost 8-fold.

Of 24 consecutive cases studied in which the electrocardiogram showed unequivocal evidence of myocardial necrosis, all but 2 showed elevation of the serum transaminase above 40 units/ml. when samples were obtained within 48 hours after the onset of pain. Typically, the serum levels rose sharply to a peak within 36 hours after the onset of pain and then fell somewhat less rapidly within 4 to 6 days. The peak values observed ranged from 54 to 308 units/ml., with a mean of 154 units/ml.

In contrast, patients with the transient myocardial ischemia of angina pectoris showed no elevation of serum transaminase levels.

The authors have observed slight elevations after abdominal surgery. Striking elevations (over 100 units/ml.) were found in cases of diffuse liver disease. On the other hand, normal levels were observed in uncomplicated cardiac failure, acute pneumothorax, pericarditis, nephrosis with marked edema, and in some cases of pulmonary infarction.

MAXWELL

Gillmann, H.: Investigations Concerning Diagnosis and Prognosis of Myocardial Infarction. Cardiologia **27:** 235 (Fasc.4/5), 1955.

A correlation is presented of clinical and postmortem findings in 250 cases of recent myocardial infarction. There were 73 cases in which the diagnosis was made only at autopsy, comprising cases of sudden death or cases in which myocardial infarction was an additional event in the course of another disease. Increased incidence of myocardial infarction in the past 7 years could be demonstrated and verified by statistical methods, and several possible causes are mentioned. The average mortality in the entire material was 32.4 per cent. When cases without QRS alterations in the electrocardiogram were excluded, the lowest mortality was found in instances of posterior wall infarction. The over-all proportion of males and females was 4:1, but this ratio tended to decrease with increasing age. Both average age and mortality were higher in females. Pain sensations during myocardial infarctions may occur practically in all parts of the trunk, extremities, and neck. The electrocardiographic alteration, while subject to great variations, remains the most important method in establishing the diagnosis.

The increasing incidence of myocardial infarction has become a major medical and social problem. Prophylaxis and therapy depend largely on a better understanding of predisposing factors leading to the disease.

PICK

Reiderer, J., and Themel, K. G.: Diagnosis and Differential Diagnosis of a Cardiac Aneurysm with Rupture and Formation of a Pseudodiverticulum of the Pericardium. Cardiologia **27:** 44 (Fasc.1), 1955.

A case of a 66-year-old man is reported who, 2 months after an anterolateral wall infarct with typical clinical and electrocardiographic course, developed another attack of severe chest pain without electrocardiographic signs of extension of the infarction. X-ray examination 2 months later and 1 week before death revealed a large bulge in the region of the left ventricle interpreted as ventricular aneurysm. Autopsy revealed that this aneurysm had perforated into the pericardium with development of a pseudodiverticulum filled with thrombi.

The authors discuss the differential diagnosis of diverticula from other unusual forms of circumscribed enlargement of the heart shadow. A localized hemopericardium leading to diverticula should be suspected in patients with ventricular aneurysm, who develop an increase in the size of the heart subsequent to an apparent recurrence of myocardial infarction, without corresponding electrocardiographic alterations.

PICK

Brofman, B. L.: Surgical Treatment for Coronary Artery Disease. Medical Evaluation of 70 Consecutive Patients. Geriatrics **10:** 511 (Nov.), 1955.

The Beck I and II operations were carried out in 70 patients. The age of the patients ranged from 28 to 72 years, with an average age of 49 years. The author details the preparation of the patient and the medical care during surgery. He emphasizes that all patients should be adequately digitalized before surgery. Of the 70 patients, 13 had the 2-stage Beck II operation, the remainder the Beck I. In the last 55 surgical patients undergoing the Beck I procedure, only 3 died, a mortality of 5.5 per cent. Forty-four patients who survived operation were followed from 9 months to 3 years, with an average of 19 months. Three patients were classified preoperatively as mild, 27 as moderate, and 14 as severe. The long-term mortality of 4.5 per cent for this group compares favorably with a predicted mortality rate of 25 per cent in a similar control group. Four of the surviving 42 patients of the follow-up group had attacks suggestive of acute myocardial infarction. Thirty-eight, or 86.5 per cent, have little or no pain; 37, or

84 per cent, are working either full time or more than before operation.

RINZLER

Milch, E., Zimdahl, W. T., Egan, R. W., Hsia, T. W., Anderson, A. A., and David, J.: Experimental Prevention of Sudden Death from Acute Coronary Artery Occlusion in the Dog. Am. Heart J. **50:** 483 (Oct.), 1955.

A standardized procedure for the production of an acute coronary occlusion in the dog is described. This method minimizes extracorporeal stimuli. The authors' objective was to study the mechanisms and etiology of ventricular fibrillation in acute coronary occlusion and to investigate methods for its prevention.

In the control series, 16, or 62 per cent, of the 26 dogs died within the first 24 hours. The effect of bilateral thoracic sympathetic ganglionectomy upon the mortality rate, was studied in 28 animals; eleven, or 39 per cent, died within the first 24 hours. The effect of procaine injection of the left stellate ganglion upon the mortality rate, was studied in 50 animals; eight, or 16 per cent, died within the first 24 hours.

It is concluded that thoracic sympathectomy and procaine injection of the left stellate ganglion protect the dog from ventricular fibrillation and death following coronary occlusion.

RINZLER

Smart, T. B., and Bruce, R. A.: Relationship of Mortality from Myocardial Infarction to Pathologic Findings and Age. Am. J. M. Sc. **230:** 380 (Oct.), 1955.

The clinical records of 160 patients with myocardial infarction admitted to a General Hospital over a 2½-year period were reviewed to evaluate pathologic findings in relation to mortality. Necropsy records were available on 69 per cent of 117 fatal cases. The Pathologic Index Rating proposed by Schnur was determined for each patient on the basis of the findings described on admission. This rating is obtained by assigning a numerical value to each clinical finding or complication known to influence unfavorably prognosis in myocardial infarction. It was found that the severity of the illness in terms of pathologic complications was more closely related to mortality from myocardial infarction than other factors, such as age. However, it was found that older patients tend to have higher Pathologic Indices. It was felt that the Pathologic Index Rating was a valid index of prognosis and should be utilized in the evaluation of effects on mortality of treatment.

SHUMAN

Katz, L. N.: The Role of Diet and Hormones in the Prevention of Myocardial Infarction. Ann. Int. Med. **43:** 930 (Nov.), 1955.

In the chick, it has been demonstrated that cholesterol feeding can readily induce coronary atherosclerosis and that various exogenous and endogenous factors can modify the course of the arterial changes thus produced. Ordinarily, regression of such atherosclerotic lesions occurs following the withdrawal of the high-cholesterol feeding. However, this regression does not occur (1) in the presence of diabetes induced by administration of adrenal cortical steroids, (2) when pancreatectomy has been performed or (3) when insulin is administered to the nondiabetic chick. When estrogens, either alone or in combination with androgen, are concurrently administered to cholesterol-fed, immature, growing male chicks, coronary atherosclerosis fails to develop. The same result occurs in the normal chick, in the chick rendered diabetic by adrenal cortical steroids, and in the depancreatized chick. In the thiouracil-treated chick, this protective action of estrogen is not observed. Furthermore, the administration of estrogen to the chick, after coronary atherosclerotic lesions have been produced by cholesterol feeding, will be followed by the disappearance of the arterial lesions. An extension of these results is the observation that cholesterol feeding to sexually mature hens is not followed by development of coronary atherosclerosis, whereas cholesterol-fed roosters develop extensive coronary atherosclerotic lesions. It is therefore evident that animal research on atherosclerosis has already yielded several new possible approaches to the care of human atherosclerotic patients and may be of importance in the prevention of myocardial infarction. Extensive clinical investigation is still necessary to determine whether these approaches will eventually find a place in general therapeutics and prophylaxis.

WENDKOS

Wright, I. S.: Present Status of Anticoagulant Therapy in the Treatment of Myocardial Infarction: the Use and Misuse of Anticoagulants; an Evaluation of New Anticoagulants, Their Indications and Dosage. Ann. Int. Med. **43:** 942 (Nov.), 1955.

Some workers believe that anticoagulants should be used only for severe cases, or for those who have already suffered thromboembolic complications; but the trend in the leading clinics with large experience with this form of therapy is the use of anticoagulants in all cases of myocardial infarction unless there are contraindications to their use. Long-term anticoagulant therapy after one or more myocardial infarctions appears to give the patient a better prognosis. However, further study and analysis are essential before this position can be accepted as absolutely conclusive. Major factors responsible for the misuse of anticoagulants include: (1) self medication without prothrombin tests; (2) medication under physician's directions but without correct control; (3) administration of anticoagulants in the face of contraindications; (4) withholding of anticoagulant therapy in the presence of definite indica-

tions; (5) excessive dosage; (6) inadequate dosage. Accumulated experience with these drugs has reduced the relative incidence of serious hemorrhage. Serious hemorrhage is rare in mild and moderately ill patients. The availability of vitamin K_1 has increased the safety. New Coumarin and phenylindandione derivatives have been introduced for clinical use, but they seem to have no advantages over Dicumarol. Heparin remains the only drug of its type suitable for clinical use. The so-called anticoagulants with enzymatic properties are thus far in an experimental phase and are not recommended for general use in man, pending much more comprehensive and critical evaluation.

WENDKOS

CONGESTIVE HEART FAILURE

Wild, J. H.: Mechanical Drainage of Massive Edema. J. A. M. A. **159:** 26 (Sept. 3), 1955.

Despite modern therapy, edema sometimes proves to be a formidable problem and recourse has to be made to mechanical means for removing excess fluid. The author describes an apparatus containing 12 needles set into a piece of cork so that their points protrude by at least a half inch. Multiple punctures of the skin can be made with this apparatus so that the patient feels as if only 1 needle is being inserted. Punctures are made in a dependent portion (preferably the dorsum of the foot or the medial and lateral aspect of the dorsum of the leg). The legs are allowed to hang in a dependent position so that fluid will run out of the puncture wounds. The author uses this method for mechanical relief when edema causes tension of the skin that is not rapidly relieved by more conservative therapy, when mercurial diuretics are contraindicated, or in order to shorten the patient's stay in the hospital. The apparatus is simple, the time taken is minimal, and the method can be employed in the patient's home when necessary.

KITCHELL

Buhr, G.: The Behavior of Intracardiac Pressures and Dynamic Cardiac Intervals under the Influence of Digoxin in the Failing Human Heart. Arch. Kreislaufforsch. **22:** 206, 1955.

As early as 5 minutes after intravenous injection of 0.75–1.0 mg. of Digoxin, the following progressive changes were observed in all cases studied: the heart rate decreased and the phase of isometric contraction became shorter while the ejection phase became longer. In 2 cases of left cardiac failure the elevated right ventricular and pulmonary pressures fell, the heart output rose, while the late diastolic right ventricular pressure rose slightly. In 2 cases of right heart failure the elevated right ventricular late diastolic pressure fell and the pulmonary artery pressure rose, while the dynamic intervals of the right ventricle showed much greater changes than those of the left ventricle. In 2 cases of bilateral failure the cardiac output rose and the pulmonary pressure showed elevation at first, then a decrease. The observations are in favor of a direct effect of the glycoside on the ventricular muscle rather than an indirect effect on the venous circulation.

LEPESCHKIN

Lindenberg, H.: Investigations Concerning the Action of Carbon Dioxide Spring Baths in Right and Left Cardiac Failure. Arch. Kreislaufforsch. **22:** 247, 1955.

Normal persons show a greater increase in the heart output (calculated from pulse pressure and velocity according to Broemser and Ranke) in a carbon dioxide bath of a subjectively indifferent temperature than in a conventional bath of this temperature. This difference, as well as the increase itself, did not appear in cases with right ventricular overload with or without failure, but were present in the majority of the cases with left ventricular overload, even with left ventricular failure. The conclusion is made that increased blood volume or resistance in the pulmonary circulation prevents the normal increase of the heart output that appears as a specific effect of the carbon dioxide bath.

LEPESCHKIN

V. Lutterotti, M.: Electrophoretic Characteristics of Plasma Proteins in Cardiac Failure. Arch. Kreislaufforsch. **22:** 170, 1955.

In 100 cases, filter paper electrophoresis was carried out. In bilateral failure there was marked increase of γ-globulins, marked decrease of the albumins, and slight increase of the β- and α-globulins. Similar changes appeared in right heart failure, except that β-globulins and α-2-globulins were little modified; the changes were parallel to the degree of failure but not to that of edema. In left heart failure the albumins were slightly decreased and the α-1-globulins were definitely elevated. If hepatic congestion persisted less than a year, the γ-globulins were not elevated but the α-1-globulins showed an increase at the expense of the albumins. In hepatic congestion of more than a year's duration the γ-globulins were elevated at the expense of the albumins, but α-1-globulins were not elevated.

LEPESCHKIN

Silverman, B. K., Breckx, T., Craig, J., and Nadas, A. S.: Congestive Failure in the Newborn Caused by Cerebral A-V Fistula. Am. J. Dis. Child. **89:** 539 (May), 1955.

Congestive failure with gross cardiomegaly is a relatively rare condition in the early neonatal period. From the etiologic viewpoint, 4 main causes have been described: developmental anomalies of the heart; primary myocardial disease; prolonged paroxysmal atrial tachycardia; and extracardiac causes of increased cardiac output (large patent ductus, severe hemolytic anemia, multiple telangi-

ectasias of the cerebral vessels). The authors describe still another, hitherto undescribed, extracardiac cause of marked cardiomegaly with congestive failure in a newborn infant. This entity, encountered in 2 autopsied cases, consists of a large cerebral arteriovenous fistula resulting in gross cardiomegaly and death.

Clinical and pathologic data are presented. Gross cardiomegaly, cyanosis, and other evidences of congestive failure suggested the clinical diagnosis of congenital heart disease in both instances. At autopsy, a large heart without structural abnormality was found in each case.

A brief review of the literature on congenital cerebral A-V aneurysms and a discussion of their circulatory effect are presented. It is proposed that congenital cerebral A-V aneurysms should be included in the differential diagnosis of newborn infants with marked cardiomegaly and congestive failure.

MAXWELL

Davis, J. O., Howell, D. S., and Hyatt, R. E.: Sodium Excretion in Adrenalectomized Dogs with Chronic Cardiac Failure Produced by Pulmonary Artery Constriction. Am. J. Physiol. **183:** 263 (Nov.), 1955.

While adrenalectomized dogs were maintained on desoxycorticosterone acetate and cortisone, they were subjected to intermittent constriction of the pulmonary artery until cardiac failure developed. The dogs were trained and unanesthetized. In failure, the cardiac output was reduced. There was an increase in mean right atrial pressure. Ascites developed. Natriuresis was observed when all replacement therapy was discontinued, and also when cortisone or DCA was used alone.

If cortisone was used to support the circulation, it was possible to study the effects of DCA on sodium excretion. Small doses of DCA (0.5–1.0 mg./day) produced a variable sodium excretion. However, on larger doses (3–25 mg./day) there was almost complete absence of sodium excretion The authors indicate that increased amounts of circulating aldosterone may be important in sodium retention in experimental heart failure when the adrenal glands are not removed. This is supported by the close relation to DCA administered and the sodium retained.

OPPENHEIMER

Bessman, A. N., and Evans, J. M.: The Blood Ammonia in Congestive Heart Failure. Am. Heart J. **50:** 715 (Nov.), 1955.

Arterial and venous blood ammonia levels were measured in 9 control patients and in 9 patients with congestive heart failure. The average arterial and venous ammonia levels of the control patients were 0.79 and 0.83 γ/ml., respectively. The average arterial and venous blood ammonia levels of patients with congestive heart failure were 1.33 and 1.06 γ/ml., respectively. Patients without liver dysfunction or congestive heart failure show normal blood ammonia values with a negligible arteriovenous difference, while patients with congestive heart failure show an elevated blood ammonia with an uptake of ammonia by the tissues. The cerebral manifestations of lassitude, lethargy, and coma seen in congestive heart failure may be due in part to ammonia intoxication, etiologically similar to the cerebral symptoms of hepatic insufficiency. It is suggested that ammonium chloride be used with caution in patients with cardiac failure presenting cerebral manifestations or severe liver dysfunction

RINZLER

Judson, W. E., Hollander, W., Hatcher, J. D., and Halperin, M. H.: The Effects of Exercise on Cardiovascular and Renal Function in Cardiac Patients with and without Heart Failure. J. Clin. Invest. **34:** 1546 (Oct.), 1955.

The authors attempted to discover whether exercise in the supine position in patients with heart disease produces the same antidiuretic and antisaluretic responses as in normal individuals.

A group (A) of 15 patients with severe and usually decompensated heart disease were studied as were a group (B) of 8 patients with chronic pulmonary disease. It was found that patients in group A had significant reduction in renal plasma flow, glomerular filtration rate, and sodium excretion. These changes were quantitatively less marked in group B. These decreases were parallel to the decreases in water, sodium, chloride, and potassium excretion.

In the recovery period the renal hemodynamic measurements returned to normal more rapidly than did sodium excretion, suggesting that sodium retention was a matter of renal tubular activity rather than the glomerular filtration rate.

The degree of cardiovascular response was not correlated with the degree or duration of reduction in renal hemodynamics or sodium excretion.

WAIFE

Judson, W. E., Hatcher, J. D., Hollander, W., Halperin, M. H., and Wilkins, R. W.: The Effects of Venous Congestion of the Limbs and Phlebotomy upon Renal Clearances and the Excretion of Water and Salt. II. Studies in Patients with Congestive Failure. J. Clin. Invest. **34:** 1591 (Nov.), 1955.

It had previously been shown that venous congestion of the limbs in both normal and hypertensive subjects causes a decrease in urine flow and sodium excretion. The present study investigated certain aspects of this phenomenon. Patients with congestive heart failure may or may not show these changes in salt and water excretion after venous congestion of the legs (cuffs on the thighs) or phlebotomy.

From various cardiohemodynamic measurements it was noted that decreases in urine flow and sodium excretion are more apt to occur if there is a decrease in cardiac output or arterial pressure, or if these are signs of imminent circulatory collapse. On the other hand, venous congestion or phlebotomy could lead to increases in sodium and water excretion if there is an increase in cardiac output or peripheral arterial pressure. It appears, then, that a suboptimal, hypovolemic, hypokinetic state of the effective circulating blood volume is an effective producer of compensating homeostatic mechanisms, including a relative decrease in water and salt excretion.

WAIFE

Parker, J. G., and Felder, L.: Jaundice in Cardiac Failure without Infarction. Ann. Int. Med. **43:** 1031 (Nov.), 1955.

Jaundice in cardiac patients does occur without infarction. It can occur secondarily to cardiac cirrhosis or necrosis of the hepatic cells. The elevated venous pressure and anoxemia in the liver in severe congestive failure can explain the resultant hepatocellular damage with necrosis and secondary cirrhosis. In addition, in severe chronic congestive heart failure there is increased red cell destruction secondary to stasis, with increased pigment deposition. This increased bilirubin formation and the extensive anatomic liver changes are the important factors in the production of the jaundice. Of the 11 patients described in this report, 10 had rheumatic heart disease and atrial fibrillation. Because of increased hazards from anticoagulant therapy in the presence of liver damage, it is recommended that anticoagulant therapy should not be instituted in cardiac patients with jaundice unless pulmonary, renal, or splenic infarction is unequivocally present.

WENDKOS

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, & BALLISTOCARDIOGRAPHY

Gallavardin, L., Finas C., and Oelbrandt, L.: Atrio-Ventricular Block and Pregnancy. Observations on Two Cases with Fatal Outcome. Arch. mal coeur **48:** 768, 1955. Abstracted, Circulation **14:** 114 (July), 1956.

Scherf, D.: The Atrial Arrhythmias. New England J. Med. **252:** 928 (June 2), 1955.

The differences between atrial and ventricular arrhythmias is discussed. As far as treatment is concerned, the atrial arrhythmias are less responsive to procaine amide and more responsive to quinidine than the ventricular ones. In general, atrial arrhythmias do not endanger life, provided complications are not present.

Atrial premature contractions are much less common than ventricular ectopic beats, however, they are not unusual in patients with coronary sclerosis, and they also occur when coronary occlusion interrupts the blood supply to parts of the atrium. They are rarely noticed as a consequence of digitalis therapy.

The author believes that a wandering atrial pacemaker is often accompanied by atrial premature contractions and that this condition demands the administration of quinidine, since it may be followed by atrial fibrillation. He accepts the distinction between atrial flutter and paroxysmal tachycardia, in spite of recent experimental results to the contrary.

ABRAMSON

Furbetta, D., Bufalari, A., and Santucci, F.: Definitions and Limits of the Electrocardiographic Characteristics of the U Wave in Normal Conditions. Folia cardiol. **14:** 338 (Aug.), 1955.

A study of the U deflection of the electrocardiogram in 100 normal individuals of both sexes and various ages is presented. The contour of the U wave and its normal variations are described. The U wave is found in all normal electrocardiograms in 1 or more leads, if the 12 routine leads are taken. The maximum height observed in this series was 0.2 millivolt; the mean duration was 0.20 sec. The relationship between U and T, the duration of Q-T and of Q-U, and other characteristics are analyzed.

CALABRESI

Bovo, G.: An Electrocardiographic Study of Cardiac Mobility by Unipolar Technic. II. Observations in Various Cardiorespiratory Affections with Special Reference to Mediastinopericardial Adhesions. Folia cardiol. **14:** 143 (Apr.), 1955.

Observations have been made in 120 patients, divided in 2 groups of 60 cases each. In the first 60 patients the technic of Cartier and Dieuaide was followed; in the second group, the unipolar limb leads and the precordial leads V_1, V_3, V_5, sometimes also V_{3R}, V_2, V_6 were added. In each series are included healthy controls, patients with extensive or limited mediastinopericarditis and pleuropericarditis, and patients with heart disease but without accretio cordis. Ten patients were operated upon and the electrocardiographic study was repeated after surgery; some others were autopsied. Among the clinical studies roentgenkymography and in some also pneumomediastinum are included. From these observations it is concluded that the test provides useful information; that the precordial leads give further data regarding translatory and rotatory movements of the heart; that in some patients with partial accretio cordis the cardiac mobility appears to be still present, and that even after successful operation the heart may remain fixed by electrocardiographic observation; that in patients with marked cardiomegaly or with pericardial effusion and without adhesions, there is no electrocardiographic evidence of cardiac mobility.

CALABRESI

Pick, A., and Katz, L. N.: Disturbances of Impulse Formation and Conduction in the Pre-Excitation (WPW) Syndrome—Their Bearing on Its Mechanism. Am. J. Med. **19:** 759 (Nov.), 1955.

The authors analyzed 5 selected cases of the pre-excitation (WPW) syndrome that exhibited various types of disturbance of formation and conduction of the cardiac impulse. In all instances the hypothesis of 1 or more anomalous A-V connections, rather than the hypothesis of an hyperexcitable ventricular focus, proved most appropriate to account for all aspects of the pre-excitation syndrome, including various simple and complex arrhythmias. This was true even in the presence of a ventricular parasystolic center. In 1 case, in which ventricular pre-excitation occurred with an abnormally prolonged P-R interval, the accessory A-V junction was considered to originate in the lower portion of, or below, the A-V node.

In another instance, intermittent spontaneous impulse formation in an accessory A-V bridge had to be postulated to account for all characteristics of the ectopic beats occurring as sporadic premature systoles or in the form of a paroxysmal tachycardia. Delayed anomalous excitation and impulse formation in the anomalous bypass, demonstrable in these 2 cases, represent 2 missing links postulated as additional evidence for the concept of an accessory A-V connection. It would appear that the anomalous muscular A-V connection present in patients with the pre-excitation syndrome has the special properties ordinarily attributed to specific cardiac tissue, viz., conductivity and rhythmicity. The property of conductivity predominates and is responsible for the common spontaneous manifestations of ventricular pre-excitation, including the various associated disorders of rhythm. The property of rhythmicity, when present, ordinarily is dormant, but in exceptional instances may become manifest and lead to isolated ectopic beats or to ectopic rhythms.

HARRIS

Caccuri, S., and Graziani, G.: The Ventricular Gradient in Bundle Branch Block. Arch. mal. coeur **48:** 1107 (Dec.), 1955.

In 40 cases of left bundle-branch block (mostly hypertension, valvular disease, and "myocarditis") the ventricular gradient ranged between −96° and +97°, with a magnitude between 4 and 73 Ashman units. Only in 13 cases did the gradient exceed the normal limits of −20° and +95° in direction, and only in 14 cases did it exceed the normal limits of 2.5 and 23 units. In 51 cases of right bundle-branch block (approximately the same clinical composition) the gradient ranged between −171° and +95° in direction and 4.3 to 88 units in magnitude. It exceeded the normal limits of direction in only 5 cases and those of magnitude in 17 cases. In 4 cases of incomplete bundle-branch block the gradient was normal. There was no relation between the values of the gradient and the clinical condition of the myocardium.

LEPESCHKIN

Caniggia, A., Bertelli, G., and Fabrizi, G.: The Maneuver of Azoulay in the Phonocardiographic Examination of Mitral Stenosis. Folia cardiol. **14:** 313, 1955.

A phonocardiogram was registered before and immediately after passive elevation of the legs in 20 cases of mitral stenosis. The intensity of the second component of the first heart sound, of the opening snap, and especially of the presystolic and diastolic murmurs was elevated in all cases, while the systolic murmur of concomitant mitral insufficiency remained unchanged. In an additional case of hypertensive heart failure, diastolic vibrations attributed to relative mitral stenosis appeared. These changes are attributed to an increase in the cardiac output and to tachycardia, but in 1 case spontaneous tachycardia did not cause them. After mitral commissurotomy the maneuver caused only an accentuation of the opening snap, but not the reappearance of the diastolic murmur; this could be induced only after many months. The Azoulay maneuver is preferable to the left lateral position in the phonocardiographic detection of initial mitral stenosis, since it does not cause any change in the position of the microphone and does not interfere with complete muscular relaxation necessary for minimal background noise.

LEPESCHKIN

Furbetta, D., Bufalari, A., and Santucci, F.: Vectorial Characteristics of the U Wave under Normal Conditions. Folia cardiol. **14:** 363, 1955.

The U-wave vectors were calculated from the 12 standard leads and special anteroposterior leads, registered synchronously 2 at a time. In the frontal plane the magnitude of the area of the U-wave vector ranged from 0 to 3 units, with an average of 0.5 units (each unit measuring 50 microvolt-second); the direction of this vector ranged between 15° and 90°, with a mode of 45° and an average of 60°. The vector loop is very narrow, and shows sometimes partly clockwise, partly counterclockwise rotation. In the horizontal plane the U-wave vector has an apparent magnitude of about 1.2 units and an apparent direction of 80°, with counterclockwise rotation of the loop; exact determination is impossible. In the sagittal plane the U-wave vector is directed anteriorly and downward, to judge by the esophageal leads, in which U shows maximal negativity 25–30 cm. from the teeth and becomes isoelectric at the 35–40 cm. level and positive below this level. In the frontal plane, when QRS waves show left axis deviation, U waves show a slightly greater tendency to left axis deviation than when QRS shows normal axis (45°–60°); when QRS shows right axis deviation, U shows a marked tendency to right axis deviation.

The same relation is present in a more pronounced form when the axes of T and U are compared; when the angle between QRS and T increases, U follows T rather than QRS. Usually U points more to the right than QRS or T. In the horizontal plane the U axis is usually about 90°, the T axis 45°, and the QRS axis 0°. With increasing age the QRS axis shows a tendency to become more horizontal while the T and U axes tend to become more vertical.

LEPESCHKIN

Jacquet, M., and Merlen, J.-F.: Arterial Carotid Peizogram and Ballistocardiogram of Cardiac Neurotonic Persons. Arch. mal. coeur **48:** 948, 1955.

Of 75 young persons with normal clinical, roentgenologic and electrocardiographic cardiac findings, who manifested palpitation, tachycardia, heart pain, vasovagal crises, and neurocirculatory asthenia, more than one-half showed normal ballistocardiograms and carotid pulses. The remainder showed hypokinetic or hyperkinetic ballistocardiograms and "bell-form" or low amplitude of the arterial pulse.

LEPESCHKIN

HYPERTENSION

Schreier, P. C., Adams, J. Q., Turner, H. B., and Smith, M. J.: Toxemia of Pregnancy as an Etiological Factor in Hypertensive Vascular Disease. J. A. M. A. **159:** 105 (Sept. 10), 1955. Abstracted, Circulation **14:** 134 (July), 1956.

Covian, M. R., and Houssay, H. E. J.: Arterial Hypertension in Hemidecorticate Rats. Circulation Research **3:** 459 (Sept.), 1955.

Arterial hypertension developed in almost all hemidecorticate rats in the course of 1 month following operation. This hypertension, which lasted no more than 2 months, could be attributed to an increased activity of the sympathetic system following release of subcortical structures from the normal modulating action of the cerebral cortex. Like other forms of experimental neurogenic hypertension, this hypertension was alleviated by bilateral adrenalectomy or by sympathicolytic drugs.

AVIADO

Heymans, C., and Delaunois, A. L.: Action of Norepinephrine on Carotid Sinus Arterial Walls and Blood Pressure. Proc. Soc. Exper. Biol. & Med. **89:** 597 (Aug.–Sept.), 1955.

Epinephrine and norepinephrine applied locally to the arterial wall of the carotid sinus provoke a marked reflex fall of the systemic arterial pressure in normal and hypertensive dogs. These drugs increase the state of contraction and tension of the arterial walls and stimulate the baroreceptors, although neither pressure nor pulsatile expansion was present in the sinuses. Changes in pulsatile expansion of the barosensitive arterial walls thus do not play a primary role in the development of baroreceptor stimulation induced by local application of norepinephrine. Changes in tone and tension of the barosensitive walls, therefore, play a primary and fundamental role in the mechanisms of reflex homeostasis of blood pressure.

AVIADO

Mohanty, M. J.: The Development of Tolerance and Cross-Tolerance to Methonium Compounds in Laboratory Animals. Brit. J. Pharmacol. **10:** 279 (Sept.), 1955.

Tolerance to the ganglion-blocking action of hexamethonium follows its administration to intact laboratory animals and seems to be similar to that observed clinically. The degree of development of tolerance in animals is related to the size and frequency of the dose. Tolerance can be demonstrated in isolated ganglion preparations obtained from animals previously treated with hexamethonium, ganglion preparations from untreated animals do not show tolerance. However, the application of blood from tolerant patients or animals to isolated ganglion preparations from untreated animals is followed by the development of tolerance at the ganglia. It seems reasonable to conclude that in the intact animal, or man, the development of tolerance is not a local reaction of autonomic ganglia to the presence of hexamethonium, but the administration of the drug to the whole animal is followed by the appearance in the blood of a substance that reduces ganglionic sensitivity to hexamethonium. The site of formation of this substance is not known.

AVIADO

Itahara, K., Fukuchi, S., Fujibayashi, T., and Yamaguchi, M.: Frequency of Essential Hypertension and the Influence of Environmental Condition Thereon. Tohoku J. Exper. Med. **61:** 231 (Feb.), 1955.

The number of essential hypertension patients on the wards showed a very remarkable drop in the last years of World War II when the food conditions in Japan fell to the lowest level. In 1950, when the food condition in Japan recovered the level of the prewar period, there were found, among some 6,000 men and women of over 20 years of age, working in various positions and appearing to be outwardly and apparently healthy, about 5.3 per cent with pressures more than 150 mm. systolic, and 1.5 per cent with marked fragility of the capillary blood vessels. The region of certain agrarian villages is reported as having the highest mortality rate by cerebral hemorrhage, not only in the mortality statistics of Japan, but also in those of the world. Among the native active population of these villages, the frequency of hypertension was found to amount to 30 per cent.

The authors conclude that the incidence of hypertension tends to rise in cold climate or season.

Smoking and the drinking of alcoholic beverages cannot be looked upon as major factors in fostering hypertension, as has been vaguely but widely believed hitherto. The authors have subjected the environmental conditions prevalent in these agrarian villages where the frequency of hypertension is registered as the highest, and in some fishing villages in Iwate Prefecture where the frequency is the lowest in Japan, to a comparative study from various points of view and draw interesting, if not valid, conclusions.

BERNSTEIN

Marks, B. L.: Aspiration Biopsy of the Kidney in the Appraisal of Unilateral Renal Disease with Hypertension: Report of a Case. M. J. Australia **1:** 684 (May), 1955.

A case is presented in which nephrectomy was performed for unilateral chronic pyelonephritis with hypertension. Aspiration biopsy of the unaffected kidney was performed prior to nephrectomy.

Renal biopsy may be of assistance in deciding against nephrectomy. This is important, since useless nephrectomy may accelerate the course and thereby prohibit effective symptomatic treatment.

Preoperative biopsy of the other kidney is especially indicated in those cases in which, despite the presence of an apparently unilateral lesion, other indications are less favorable; such as age (over 50 years) and hypertension of long standing.

BERNSTEIN

PATHOLOGICAL PHYSIOLOGY

Albers, C., Brendel, W., and Usinger, W.: Circulation, Respiratory Metabolism and Respiration in Ether Narcosis. Arch. exper. Path. & Pharmakol. **226:** 278 (Aug.), 1955.

The effect of ether narcosis on circulation, respiration, and respiratory metabolism were studied in 214 experiments in 6 dogs. Sphygmographic methods (Wezler-Boeger) were used for the study of circulation; volume and rate of respiration, oxygen consumption, and CO_2 elimination were measured; the reactivity of circulation was tested by the carotid sinus reflex and by the reaction to injection of epinephrine and to inhalation of pure oxygen and of 4 to 8 per cent CO_2 admixture to air; the depth of narcosis was gaged by a series of somatic reflexes. As compared with the resting state, in ether narcosis the cardiac rate was greatly increased, the mean arterial pressure was slightly reduced, the pulse pressure and the stroke volume were markedly reduced, the output per minute was increased; the elastic resistance was increased, and the peripheral resistance was slightly reduced. The carotid sinus reflex was depressed by narcosis, as was the response to epinephrine and to inhalation of oxygen or of CO_2. The minute volume and the rate of respiration increased during ether narcosis; the mild hypoxia was probably due to the high concentration of ether vapor in the inspired air. The oxygen consumption was increased, due to the increased work of respiration. It is concluded that the circulatory effects of ether result from adaptation to the oxygen demand, to depression of regulatory reflex mechanisms, and to hypoxia. The differences noted between ether and Pernocton narcosis are interpreted as due to the peripheral vasodilator and the central analeptic effects of ether.

CALABRESI

Gehl, H., Graf, K., and Kramer, K.: The Pressure Volume Diagram of the Heart of Cold-blooded Animals. The Significance of the Plastic Element for Cardiac Mechanics. Pflüeger's Arch. ges. Physiol. **261:** 270 (July), 1955.

The pressure volume diagram of the ventricle is studied under conditions of increasing plastic dilatation in more than 100 isolated hearts of *Rana esculenta* or *temporaria*. The distensibility curves of the relaxed ventricle show a flat segment at low pressure, followed by a steep ascent at pressures of 3 to 4 cm. H_2O. Repeated measurements show increasing distention, so that the increase in volume may amount to 30 per cent of the initial volume. In isometric contraction, marked dilatation occurs at pressures above 30 cm. H_2O. The isotonic contraction does not influence the distention curve at rest, nor does it cause a regression of previously produced dilatation. Within the normal range of dilatation the heart empties almost completely in isotonic contractions; as an effect of plastic dilatation the stroke volume increases. The pressure volume curve is recalculated in terms of tension and length and the well-known effect of the spheric distribution of the cardiac muscle is shown again. It is shown that the curve of maxima is not influenced by fatigue. The redrawing of the pressure and volume values in terms of tension and length shows that the Frank's maximum corresponds to the maximum of pressure without essential loss of emptying. The application of these findings to the normal circulation of the frog is thoroughly considered.

CALABRESI

Lendrum, F. C.: The "Pulmonary Hyaline Membrane" As a Manifestation of Heart Failure in the Newborn Infant. J. Pediat. **47:** 149 (Aug.), 1955.

A summary is presented of evidence that "Pulmonary Hyaline Membrane Disease" in the premature infant is a manifestation of left ventricular failure. The pathologic features are interpreted as manifestations of the remarkable processes in the newborn lung for clearing alveolar fluid, and its ability to revert to a fetal type circulation with opening of right-to-left shunts as a response to pulmonary hypertension. Emphasis is laid upon

he time sequence of these events. A plea is made o treat these infants for left ventricular failure.

HARVEY

Pew, W. L.: Cardiac Arrest during Exchange Transfusion. J. Pediat. **47:** 645 (Nov.), 1955.

A case report is presented of an erythroblastotic nfant who developed cardiac arrest during an exhange transfusion. After emergency thoracotomy he infant's heart was massaged and adrenalin was dministered with recovery. The factors thought to be responsible for the cardiac arrest were cooling of the heart by the administered blood and lowering of serum Ca^{++} by the anticoagulant solution, citrate, used in the bottled blood. The measured serum Ca level drawn at the time of cardiac arrest was very low, 2.8 mEq./L. The patient, during the week following exchange transfusion, exhibited several episodes of tetany that responded to administration of calcium by the intravenous route.

HARVEY

Bugaro, L., Dalla Volta, S., and DeCastro, B.: Cardiac Catherization in Idiopathic Dilatation of the Pulmonary Artery. Arch. mal. coeur **48:** 721, 1955.

In 1 case, in which operation disclosed dilatation of the pulmonary artery without other abnormalities, the right ventricular pressure was 103/11 mm. Hg, with a gradual descent as the pulmonary capillaries were reached. The electrocardiogram showed right bundle-branch block with right ventricular hypertrophy. The arterial oxygen saturation was slightly decreased; the calculated heart output and pulmonary vascular resistance were normal. Two other cases, without anatomic confirmation, showed similar findings.

LEPESCHKIN

Greisheimer, E. M., Ellis, D. W., Stewart, G., Makarenko, L., Thompson, K. T., and Oleksyshyn, N.: Cardiac Output by Cuvette Oximeter under Thiopental Sodium and Cyclopropane-Oxygen Anesthesia. Am. J. Physiol. **182:** 145 (July), 1955.

Cardiac output increases under thiopental but becomes less when cyclopropane is added. The heart rate becomes slower when the volatile anesthetic is used, and blood pressure falls. Under thiopental, the peripheral resistance is low but increases markedly when cyclopropane is superimposed.

OPPENHEIMER

Nichols, H. T., Likoff, W., Goldberg, H., and Lisan, P.: The Relation of Valve Function to the Genesis of the Sharp First Sound in Mitral Stenosis. Am. Heart J. **50:** 577 (Oct.), 1955.

The authors were able to examine the events of closure of the mitral valve in the living patient during mitral commissurotomy. They observed modification in mitral stenosis of 2 events in the closure of the valve: the contracting force of the cusps, and the intra-atrial displacement of the leaflets. The striking force of the free edges of the cusps is consistently decreased in mitral stenosis and is not related to the production of a sharp first sound. Abrupt intra-atrial displacement of the leaflets is the only factor in mechanical function related to the production of a sharp first sound. Abrupt intra-atrial displacement is the result of a decrease in the length and mass of valvular tissue and an increased leaflet tension, which in turn accounts for the high pitch of the sharp first sound. The fibroblastic proliferative change in the stenotic mitral valve increases the inherent inertia of the tissue and accounts for the short duration of the sharp first sound. When extensive fibrosis or calcification converts the mitral valve to a diaphragm, intra-atrial displacement does not occur and the first sound is not sharp. The first heart sound is delayed in relation to the ventricular isometric period when intra-atrial displacement is abrupt, but is normal and independent of the rigidity of the valve, when the ballooning effect does not occur. When the first sound is delayed, the presystolic accentuation of a mid or late diastolic murmur is actually systolic in time.

RINZLER

Beneus, B., and Carlsten, A.: Effect of Intermittent Positive-Pressure Ventilation on Cardiac Output in Poliomyelitis. Acta med. scandinav. **152:** 19 (July 29), 1955.

The authors studied the effect of intermittent positive-pressure ventilation upon cardiac output during spontaneous breathing and during different forms of intermittent positive-pressure ventilation in 7 patients with acute poliomyelitis and in 2 additional totally paretic patients in whom 2 types of intermittent positive pressure ventilation were compared.

The cardiac output was found to be greater during spontaneous breathing than during intermittent positive-pressure ventilation, and it remained low on change-over to a second form of intermittent positive-pressure ventilation. When the patient was returned to spontaneous breathing, the cardiac output rose once more. It was found that a positive-pressure phase of about one third of the respiratory cycle gave a smaller reduction in the cardiac output than a positive-pressure phase lasting one half of the cycle. The factors that may be responsible for the reduction in the cardiac output include the increase of pressure in the right atrium during the positive-pressure phase and a reduction in the blood volume in the lungs resulting from this fall in the pressure gradient of the venous flow into the right side of the heart together with a rise in the pressure-gradient for

the blood from the lungs to the left side of the heart.

Technics that may tend to overcome the reduction of the cardiac output during intermittent positive-pressure ventilation include both the creation of negative pressure in the trachea during the expiratory phase, thereby lowering the right atrial pressure and lowering the head of the patient.

ROSENBAUM

Steinmann, B., Jaggi, U., and Widmer, J.: The Effects of Sounds and Noise on the Blood Pressure in Man. Cardiologia **27:** 223 (Fasc. 4/5), 1955.

In 33 persons, 20 to 70 years old, the effect of acoustic stimuli on the behavior of the blood pressure was studied. The brachial arterial pressure was recorded continually (method of Wagner) during a control rest period and during back-playing of tape recordings of various sudden and continuous noises, sounds, in part reproductions of car or railroad noises and of different types of music (jazz or classical). A distinction was made between purely acoustic effects, and those precipitating certain emotional associations. It was found that transient blood pressure variations (mostly elevation) occurred under both circumstances. Pure acoustic phenomena thus effective were high pitched, humming, metallic or knocking noises, and noises produced by cars. Other types of noises led to blood pressure changes only in conjunction with sudden fright reactions. The present study did not permit conclusions as to a relationship of persistent blood pressure elevation to temporary alterations produced in this manner.

PICK

Vander Straeten, M., Pannier, R., Van Loo, A., Vuylsteek, K., Verstraeten, J., and Uyttenhove, P.: A Comparative Study of Ventilatory and Hemodynamic Disturbances in the Course of Mitral Stenosis. Acta. cardiol. **10:** 443 (Fasc. 5), 1955.

In 25 patients with mitral stenosis, data of pulmonary function tests were compared with the results of cardiac catheterization. The material was divided into 4 groups according to the degree of dyspnea, in conformity with criteria of the New York Heart Association.

None of the studied cases was in the asymptomatic class I. Cases of class II had normal values with respect to maximal breathing capacity and the Tiffeneau test. Hemodynamically they revealed only a slight increase in pulmonary arterial pressure. Cases falling into groups III and IV had a markedly diminished vital capacity, maximal breathing capacity, abnormal Tiffeneau values, and an increased ratio of residual volume/total capacity. However in class II several cases were found with normal ventilatory function tests despite a severe degree of mitral stenosis. In the evaluation of cases of class IV, the result of catheterization (pulmonary hypertension, pulmonary vascular resistance, and reduction of cardiac output) proved more significant than the respiratory data.

In 11 cases biopsies were obtained from the lingula and histologic specimens were compared with the results of cardiorespiratory function tests. No correlation could be established between pulmonary hypertension and findings of arterial medial hypertrophy, between interalveolar fibrosis and hypoxemia, and the histologic demonstration of emphysema and abnormal pulmonary function tests. On the basis of their investigations the authors present a classification of cardiac dyspnea with a tabulation of pathogenetic factors.

PICK

Scott, R. C., Kaplan, S., and Stiles, W. J.: Observations on the Effect of Tetraethylammonium Chloride on the Pulmonary Vascular Resistance in Mitral Stenosis. Am. Heart J. **50:** 720 (Nov.) 1955.

The effect of tetraethylammonium chloride (TEAC) on the pulmonary artery pressure, pulmonary vascular resistance, and cardiac output was studied in 6 patients with mitral stenosis. The administration of TEAC produced a significant lowering of mean pulmonary artery pressure in 5 of 6 cases. This was due to a decrease in cardiac output in 2 cases and to a decline in pulmonary vascular resistance in 3. These results suggest that at least in some cases of mitral stenosis a portion of the increase in pulmonary vascular resistance is mediated through the autonomic nervous system. Two of these patients were also studied after mitral valvulotomy. The mean pulmonary artery pressure and the pulmonary vascular resistance were found to be lowered in both patients after surgery (to a value lower than that obtained with TEAC before surgery). The pulmonary artery pressure and pulmonary vascular resistance fell even further in both patients after TEAC.

RINZLER

Beaconsfield, P., and Ginsburg, J.: Effect of Changes in Limb Posture on Peripheral Blood Flow. Circulation Research **3:** 78 (Sept.), 1955.

Venous occlusion plethysmography was employed to measure the blood flow through the calf, foot, or hand in 6 normal subjects and 12 patients admitted to the hospital for sympathectomy. The blood flow in the normal limb was first determined with the limb in the horizontal position. The blood flow fell from this basal horizontal level when the limb was placed in a dependent position of 45 degrees or was elevated to 45 degrees, but was increased when the limb was kept in a position of elevation of 15 degrees. These findings were observed in normal limbs as well as those in whom sympathectomy was

to be performed. After sympathectomy similar changes in flow with position of the limb were found. These reactions are regarded as arising from local vascular responses to postural changes.

SAGALL

Drury, A.: The Effects of High Cholesterol Diet Alone and Plus Cortisone Administration on Phospholipid Turnover and Lipid Partition in Plasma, Liver and Aorta of Rabbits. Am. J. M. Sc. **230:** 427 (Oct.), 1955.

The lipid partition and plasma phospholipid turnover rates in plasma, liver, and aorta were measured in 3 groups of experimental animals. The first group received a control diet; the second, a diet supplemented with 1 per cent cholesterol and the third, a high cholesterol diet plus daily cortisone injections. The duration of the experiment was 35 days, corresponding to one half the time usually employed to produce atheromata, in order to evaluate the lipid-metabolic pattern prior to atheromata formation and to study the mechanisms involved in their pathogenesis. In the animals receiving cholesterol, with or without cortisone, a small but significant increase in aortic cholesterol was found. The cholesterol and phospholipid patterns in plasma were similar in these 2 groups; however, the neutral fat content of liver and plasma in the cortisone-treated group was markedly elevated. The phospholipid specific activity of liver was similar in the 3 groups of animals; however, the amount of radioactive phospholipid in plasma was greater in the cortisone-treated group than in the other 2 groups. The implications of these and other data presented are discussed in relation to the general problem of the pathogenesis of atherosclerosis.

SHUMAN

Jacoby, J., Ziegler, C., Hamelberg, W., Mogg, A., Klassen, K., and Flory, F.: Cardiac Arrhythmia: Effect of Vagal Stimulation and Hypoxia. Anesthesiology **16:** 1004 (Nov.), 1955.

The relationship of the cardiac arrhythmias induced by the vagal stimulatory effects of endotracheal intubation and hypoxia was studied in 121 patients. Blood oxygen saturation was continuously observed by means of an ear oximeter that was attached to the patient prior to the induction of anesthesia. Cardiac action was observed by electrocardiograms recorded prior to the induction, following induction, and after intubation. The blood oxygen saturations were correlated with the electrocardiogram. Hypoxia was produced in some patients by the inhalation of gas mixtures low in oxygen content and in others was frequently observed when the intubation was performed by beginning students. These studies showed that cardiac arrhythmias were produced in 9 per cent of well-oxygenated patients by endotracheal intubation and in 36 per cent of the most hypoxic patients. Thus, the cardiac responses to vagal stimulation are more frequent and more serious in the presence of hypoxia.

SAGALL

Raab, W.: Neurogenic and Hormonal Hypotension. Anesthesiology **16:** 78 (Sept.), 1955.

Various neurologic and hormonal factors are concerned in the pathogenesis of acute and sustained hypotension. These involve alterations of the neural and hormonal factors responsible for the maintenance of a normal vascular tone, cardiac output, or circulatory blood volume. The clinical forms of hypotension are due to a diminution of peripheral vascular tone caused by a primary decrease of sympathetic tone, a diminished vascular reactivity to the intrinsic adrenosympathogenic catecholamines (notably norepinephrine), an increased and exaggerated vasodilatory cholinergic effect on the vascular walls, or an increased local dilating effect of epinephrine in certain vascular areas. The primarily cardiogenic forms of hypotension result from a diminished cardiac output due to the marked slowing of the heart resulting from increased cholinergic cardio-inhibitory actions, the poor ventricular filling associated with increased sympathetic influence, or the myocardial weakness induced by catecholamine injury or electrolyte disturbances. Hypovolemic hypotension is caused by blood pooling in hypotonic vascular areas or by dehydration, as in adrenal insufficiency or diabetic acidosis. The various clinical hypotensive conditions in which these mechanisms are involved are reviewed and the guiding principles of therapeutic correction of the different pathogenic types of neurogenic and hormonal hypotension are considered.

SAGALL

Bader, R. A., Bader, M. E., Rose, D. J., and Braunwald, E.: Hemodynamics at Rest and During Exercise in Normal Pregnancy as Studied by Cardiac Catheterization. J. Clin. Invest. **34:** 1524 (Oct.), 1955.

The cardiac output in pregnancy was found to be increased in previous studies with gasometric methods. In this study cardiac catheterization was performed in 46 normal women from 14 weeks of gestation to term.

The average oxygen consumption was found to be slightly increased, the arteriovenous oxygen difference reduced, and the cardiac output elevated, with a peak in the twenty-fifth to twenty-seventh weeks of gestation, after which it fell toward normal as term approached.

It appears that redistribution of blood, senescence of a placental A-V shunt, or both factors may explain the fall in cardiac output at term. "The concept of obliteration of portions of the placental circulation is supported by the finding of a decreased total

peripheral resistance during the second trimester, with a progressive return towards normal at term."

WAIFE

Elkinton, J. R., Singer, R. B., Barker, E. S., and Clark, J. K.: Effects in Man of Acute Experimental Respiratory Alkalosis and Acidosis on Ionic Transfers in the Total Body Fluids. J. Clin. Invest. **34:** 1671 (Nov.) 1955.

Some metabolic effects of respiratory alkalosis (from hyperventilation) and acidosis (CO_2 inhalation) were studied in great detail in 12 normal adult men. Direct calculations of sodium and potassium transfer were made and indirect calculations of transfers of intracellular hydrogen were performed.

The results indicate that both acute hyperventilation and CO_2 inhalation are buffered to a large extent by a series of linked ionic exchanges in the extracellular fluid. Thus, in respiratory alkalosis hydrogen left the cells and was replaced by sodium. To a lesser extent, the opposite findings were present in respiratory acidosis. Changes in cellular potassium were much less extensive. These results indicate the major role of intracellular ionic transfers in buffering extracellular pH changes in acid-base disturbances. Ninety per cent or more of the change in effective extracellular bicarbonate was extrarenal, and was related to buffer activities of serum protein and to ionic transfer in and out of cellular fluid. In the past, the renal acid-base regulation and the hydrogen ion blood-buffer systems have received much attention; this study emphasizes the intracellular buffer systems.

WAIFE

Keys, A., Anderson, J. T., and Mickelsen, O.: Serum Cholesterol in Men in Basal and Nonbasal States. Science **123:** 29 (Jan. 6), 1956.

Serum cholesterol determinations are usually made on samples obtained under basal, fasting conditions. This study assessed the significance of these conditions. Determinations on normal adults revealed an average nonbasal (mid morning) value of 3.8 mg./100 ml. higher than the basal value. This difference was only 1.9 per cent of the mean basal level.

Although eating breakfast led to a small rise in cholesterol levels, this change did not occur when breakfast was followed by moderately vigorous physical work. The highest differences, 15 mg/100 ml., were found in sedentary individuals 7 hours after a breakfast (to which 10 Gm. of cholesterol was added to scrambled eggs). Under the same circumstances physical activity led to a rise of 9.3 mg./100 ml.

The authors believe these results suggest a reason for part of the difference in susceptibility to coronary heart disease between active and inactive men.

WAIFE

Kleinfeld, M., Stein,. E, Magin, J., and Kossmann, C. E.: The Action of Iodoacetate on the Electrical and Mechanical Activities of the Isolated Perfused Frog Heart. J. Clin. Invest. **34:** 1802 (Dec.), 1955

Iodoacetate in low concentrations blocks glycolysis by inhibiting an enzyme (triosephosphate dehydrogenase). In higher concentrations a general sulfhydryl inhibition has been reported. In this study the effects of low concentrations of iodoacetate on electric and metabolic activity of single ventricular fibers of isolated perfused frog hearts were observed.

The early changes consisted of a shortening of the duration of the action potential. Associated findings were a shortened S-T interval and abnormal T waves. Later a prolongation of the P-R interval was occasionally seen. The addition of intermediate substrates, such as pyruvate and acetate, produced only a partial recovery. This suggests that iodoacetate has actions other than specific inhibition of the dehydrogenase enzyme. The repolarization phase of the action potential was influenced at about the same time as the cardiac output and stroke volume. The authors postulate that the enhanced repolarization is associated with an increased migration of potassium ions out of the cell during electric activity.

WAIFE

Rose, J. C., Cosimano, Jr., S. J., Hufnagel, C. A., and Massullo, E. A.: The Effects of Exclusion of the Right Ventricle from the Circulation in Dogs. J. Clin. Invest. **34:** 1625 (Nov.), 1955.

Because of reports suggesting that an actively functioning right ventricular muscle is not necessary for the maintenance of adequate blood flow through the low pressure pulmonary circulation, the authors reinvestigated this problem. Grafts were prepared from pig or calf aorta. In 4 dogs the grafts connected the right atrium and main pulmonary artery; in 2 dogs the shunts were placed between the superior vena cava and the main pulmonary artery; and in 13 dogs shunts were placed between both vena cavae and the pulmonary artery. It was possible, by the technics described in detail in the paper, to produce 3 effective venopulmonary shunts.

The conclusion from these experiments is that the central venous pressure cannot force an adequate flow of blood through the lungs in the intact animal without benefit of the right ventricular pump. Acute occlusion of the normal blood pathway through the right ventricle results in a marked fall in systemic arterial pressure and elevation of venous pressure. Even when the venous pressure was elevated (by infusions) to levels above the normal mean pulmonary artery pressure, perfusion of the lung through these shunts proved inadequate. It would seem that previous attempts at destroying the myocardium of the right ventricle did not abolish right ventricular function.

WAIFE

PHYSIOLOGY

Mann, G. V., Teel, K., Hayes, O., McNally, A., and Bruno, D.: Exercise in the Disposition of Dietary Calories. Regulation of Serum Lipoprotein and Cholesterol Levels in Human Subjects. New England J. Med. **253:** 349 (Sept. 1), 1955. Abstracted, Circulation **14:** 89 (July), 1956.

Nelson, C. V.: Effect of the Finite Boundary on Potential Distributions in Volume Conductors. Circulation Research **3:** 236 (May), 1955.

Potential distributions in electrolytic tank models can be quickly and easily measured by use of a constant-current electrode supply and a differential voltmeter. Polarization troubles are avoided by using a 500-cycle supply, by isolating the measuring circuit from the supply circuit, and by using a very high input impedance in the voltmeter.

The "double-layer" electrolytic tank has a very small boundary error and provides a reference point of 0 potential for any source distribution. With this tank it was shown that the field of 2 halfshells is similar to the field of a dipole at remote points.

When the conducting medium has a finite boundary in the form of straight lines or circles, the potential distribution can be calculated by means of images. An application of the method shows that when a dipole is in the presence of a finite boundary, the 0 potential locus is *not* along the dipole transverse axis, and the points of maximum potential on the boundary are *not* located along the dipole axis, in the general case.

MAXWELL

Zilversmit, D. B., McCandless, E. L., and Shore, M. L.: Phospholipid Metabolism in Various Tissues of Cholesterol-Fed Rabbits. Proc. Soc. Exper. Biol. & Med. **89:** 48 (May), 1955.

To investigate the possible relationship between phospholipid turn-over rate and tissue-lipid accumulation, the authors studied the effect of cholesterol feeding on liver, lung, small intestine, kidney, muscle, aorta, and plasma. The study was done on albino rabbits injected with P^{32}.

Rabbits maintained on an atherogenic diet for 5 months showed a marked increase in the incorporation of radioactive phosphate into the phospholipids of aorta, plasma, and the whole liver. In contrast, the feeding of cholesterol and fat did not appear to have an appreciable effect on phospholipid synthesis in lung, small intestine, kidney, and muscle. The livers of the cholesterol-fed animals showed a marked increase in tissue mass over and above that caused by fatty infiltration; other organs except aorta did not exhibit significant changes in weight. A possible relationship between fatty infiltration and phospholipid turn-over is discussed.

MAXWELL

Jackson, D. E.: A Special Method for Recording the Actions of the Heart: The Cairivibograph and the Vibogram. Anesthesiology **16:** 536 (July), 1955.

The author describes a method for recording the air vibrations that are produced within the lungs and respiratory passages by the beating of the heart and the circulation of the blood within the heart, lungs, and chest cavity. The term "cairivibograph" is applied to the various forms of pick-up devices employed to record these vibrations, "cairivibogram" or "vibogram" to the records so produced, and "cairivib" waves to the air waves themselves. The device employed here utilizes a face mask that has a special breathing valve from which a rubber tube passes to the vibograph. When the lid of this valve is closed and the patient holds his breath for 5 to 10 seconds, the cairivib air waves produced within the chest are transmitted through the rubber tubing to the vibography. This generates a vibrating electric current corresponding to the beating of the heart that can be recorded through lead I of the electrocardiograph. The method described can be used in both human and animal investigations. The character of the cairivib waves and, therefore, of the vibogram itself depends on many factors: the heart; the lungs; the movements of blood within the heart, lungs, and chest cavity; and the status of all the blood vessels within the chest. The author suggests that the various waves recorded in the vibogram be numbered consecutively and also that records made by this method should be correlated with the ballistocardiogram rather than the electrocardiogram. The application of this method to the study of anesthetic drugs and other substances acting on the circulation or respiration is discussed.

SAGALL

Roddie, R. A.: Effect of Arm Position on Circulation through the Fingers. J. Appl. Physiol. **8:** 67 (July), 1955.

Previous studies have suggested that when a limb is lowered below heart level there is a greater volume flow of blood in the dependent than in the horizontal limb. Digital blood flow studies using venous occlusion plethysmography have yielded confusing results. In the present experiments the effect of arm position on circulation through the fingers was studied with a colorimetric method to assess changes in blood flow. Heat elimination from the fingers was not changed when they were raised from a fully dependent position to a level 15 cm. above the sternal angle.

Studies were made on 19 healthy young men comfortably seated. Heat elimination from the fingers of both hands was measured by a colorimeter (Greenfield and Shephard 1950). The fingers were 4 cm. above the sternal notch for the reference readings. Readings were also taken when the fingers were raised to levels 11 or 38.5 cm. above or lowered to levels 7.5, 24, 44, or 68 cm. below the plane.

Raising the fingers 11 cm. significantly decreased heat elimination to 89.7 ± 2.8 per cent of the control; raising them 38.5 cm., significantly decreased heat elimination to 43.4 ± 4.3 per cent. In all positions below the reference point, the mean rate of heat elimination was significantly greater than the reference figure, but these increased rates were not significantly different from each other. Therefore, it is impossible to say whether the rate of heat elimination depends on the distance of the fingers below the sternal notch. The responses were similar in subjects in whom peripheral vasomotor tone had been released by indirect heating.

The increased rate of heat elimination from the dependent fingers is considered to indicate an unaltered or slightly increased rate of blood flow. In no experiment was there any reduction in blood flow through dependent fingers.

WECHSLER

Rosensweig, J.: The Effect of the Position of the Arm on the Oxygen Saturation of the Effluent Blood. J. Physiol. **129:** 281 (Aug.), 1955.

The relationship between the posture and the blood flow of a limb has been investigated by various methods. Most studies suggested an increase in blood flow when the extremity was lowered.

In the present study, blood samples were withdrawn from a superficial vein of the forearm or the median cubital vein in 7 healthy young men when the arm was in the horizontal position and then in the dependent position. The O_2 content of the blood was determined by the volumetric method of Peters and Van Slyke.

The results indicated that a lowering of the arm caused an increase in the O_2 saturation of blood in the veins. The mean increase was 7.04 per cent ± 1.63 ($p < 0.01$) in the superficial veins and 16.7 per cent ± 1.52 ($p < 0.001$) in the median cubital vein. These increases were maintained for several minutes. There was some variation in O_2 saturation of arm veins when the arm remained in 1 position, however, this variation was not significant.

If it is assumed that the O_2 consumption of the limb and the arterial O_2 saturation are unaffected by the change in posture, it is reasonable to conclude that lowering the arm produces an increase in the blood flow through the tissues. It is postulated that lowering the arm decreases the resistance to flow and this allows the rate of flow to increase. Previous studies have reported a decrease in resistance to flow when the arm was moved to a dependent position.

These studies indicate that there is a higher O_2 saturation of blood from arm veins when the arm was in the dependent position. This elevation was attributed to an increase in arm blood flow that was thought to be due to distension of vessels and thus a lowering of resistance.

WECHSLER

Shephard, R. J.: The Carbon Dioxide Balance-Sheets of the Body: Their Determination in Normal Subjects and in Cases of Congenital Heart Disease. J. Physiol. **129:** 142 (July), 195

The hyperventilation produced by breathing a moderate percentage of CO_2 is not of rapid onset, and often a considerable time may elapse before respiration reaches a steady maximum level. During this interval, CO_2 gradually accumulates in the body, and a steady state may be pictured where accretion of this gas produces sufficient increase of ventilation to restore the normal metabolic output of CO_2. The time required to reach such a steady state is unknown; therefore, the exact intake and output of CO_2 at different stages during the course of experimental hypercapnia was measured.

Nine normal subjects and 22 patients with congenital heart disease breathed 5 per cent CO_2 in air or oxygen. The expired air was collected in Douglas bags and the CO_2 content of these bags and the inspiratory bag was measured by the standard Haldane gas-analysis apparatus. Alveolar and arterial CO_2 and pH were measured.

There was a large variation in the accretion of CO_2 in normal subjects. The rate of accretion was fairly steady after the first few minutes, indicating that equilibrium had been reached between the arterial blood and the tissues of the respiratory center, even though the level of hyperventilation was not yet sufficient to prevent further accretion of CO_2. The ratio of increase of ventilation to accretion of CO_2, EV/A, at this stage should give an indication of the sensitivity to CO_2 mixtures. For the first minute the EV/A ratio is low, since there is a relatively large accretion of CO_2 in the lungs and arterial blood with little change in the respiratory minute volume. In the second minute the EV/A ratio rises as the CO_2 reaches the respiratory center and stimulates ventilation. Following this the ratio falls as equilibrium is established between the respiratory center and arterial blood and the CO_2 is distributed to tissues with a poorer blood supply. In most subjects the ratio is constant after 30 minutes of hyperventilation but varies within each individual and between individuals. Between 1000 and 2000 ml. of CO_2 are retained after 30 min. breathing 5 per cent CO_2 and the change of pH can be calculated from the amount of CO_2 retained. Most of this retained CO_2 is in the body tissues other than the lungs or blood.

In the patients with congenital heart disease the amount of CO_2 accretion seems greater, hyperventilation tends to develop less rapidly, and the EV/A ratio is unchanged when compared to the average for normal subjects. These results indicate that the sensitivity of the respiratory center is within normal limits in congenital heart disease.

The steady state was not reached in these studies that were terminated after 30 min.

WECHSLER

RHEUMATIC FEVER

Roantree, R. J., and Rantz, L. A.: Clinical Experience with the C-Reactive Protein Tests. Arch. Int. Med. **96:** 674 (Nov.), 1955.

Experience with the C-reactive protein in 443 general medical cases and 50 normal controls is reported. Some comparisons are drawn between the results of this test and the results of the erythrocyte sedimentation rate, leukocyte count, and temperature recordings in the same patients. The C-reactive protein was rarely present in the serum of a person in whom no inflammatory or necrotizing process could be found. It was consistently found in the sera of patients with bacterial infections, active rheumatic fever, acute myocardial infarct, and widespread malignant disease. It was commonly, but not so consistently, found in cases of active rheumatoid arthritis, virus infection, and active tuberculosis. It was rarely present in cases of limited primary carcinoma, uncomplicated chronic leukemia, multiple myeloma, and widespread superficial dermatitis.

The C-reactive protein test gave fewer "false positive" reactions than the other indices of inflammation with which it was compared and, in general, gave a better positive correlation with inflammatory or necrotic processes. It did not give so good a positive correlation with active tuberculosis as did the erythrocyte sedimentation rate. A distinct advantage of the C-reactive protein test is that no interpretation of normal range is necessary. Any positive reaction may be considered abnormal.

BERNSTEIN

Mouquin, M., Gras, H., and Colvez, P.: On the Post-Commissurotomy Syndrome. Arch. mal coeur **48:** 758, 1955.

Three personal cases of this syndrome are described. Against the interpretation of this syndrome as a recurrence of the original rheumatic reaction are its appearance in persons who had never exhibited such a reaction previously, the rare articular involvement and prolongation of the P-R interval, and absence of an increase of the antistreptolysin titer and additional valvular involvement. On the other hand, the fact that this syndrome never appears after cardiac operations for coronary or congenital heart disease would be in favor of the above interpretation.

LEPESCHKIN

Radner, S.: Suprasternal Pressure Curves in Mitral Insufficiency. Acta med. scandinav. **152:** 1, (July 29), 1955.

The author describes a suprasternal puncture technic for the study of hemodynamic alterations in 5 cases. Pressure curves have been obtained from the aortic arch, pulmonary artery, and left atrium by direct puncture in 5 cases of mitral insufficiency. The normal aortic pressure curve is characterized by a high pressure level, a steep anacrotic rise to a rounded summit and a catacrotic incisure on the upper half of the curve. The normal pulmonary artery pressure curve shows a similar pattern when the pressure level is lower, the catacrotic incisure is placed more deeply, on the lower half of the curve, and the valvular rebound wave after the incisure is higher. The normal left atrial pressure curve consists of an initial small A wave due to atrial contraction followed by first and second sound waves separated by an intersonic dip.

In patients with mitral insufficiency the left atrial pressure curve displays a peaked second sound wave. In this disorder the pulmonary artery curve is altered by the presence of a wave or shoulder superimposed upon the upper part of the descending limb of the curve; this may be due to the retrograde propagation through the pulmonary capillaries of the peaked second sound wave from the left atrium into the pulmonary artery. The aortic pressure curve shows a low and narrow head, that is, the area above the horizontal level of the lowest point of the incisure is reduced in amplitude and duration. The author feels that these alterations in the pressure curves recorded by this technic are consistent enough that they may be used as a positive index of the degree of mitral regurgitation complicating mitral stenosis.

ROSENBAUM

ROENTGENOLOGY

Giulio, L.: Investigations on the Cardiopneumogram (Cardiopneumatic Oscillations) in Man. Arch. di fisiologia **55:** 121 (June), 1955.

The cardiopneumogram in apnea is studied in 2 subjects, 1 normal and 1 with a tracheal cannula, due to laryngectomy. The contour of the cardiopneumatic oscillations is described. The quantitative parameters and the timing of the cardiopneumatic deflections in relation to the cardiac cycle are reported. The relationships of the cardiopneumogram with the respiratory dead space, with the stroke volume of the left ventricle, and with the venous inflow are presented. The possible interference of the cardiopneumatic oscillations on the pulmonary capillary tracings and on the measurement of viscous and turbulent resistance of airflow is discussed. As the cardiopneumogram results from the difference between thoracic inflow and outflow of blood and from the systolic expansion of intrathoracic vessels, it is not possible to infer from it even an approximate value for the cardiac stroke volume.

CALABRESI

Riches, E. W.: The Present Status of Renal Angiography. Brit. J. Surg. **42:** 462 (March), 1955.

The history, technics, dangers, indications, and contraindications of renal angiography are reviewed. The lumbar route is favored over the femoral as being easier, quicker, and less prone to failure or complications. The femoral route is indicated if an

aortic aneurysm is suspected. It is a safe procedure and can be mastered fairly easily. The main cause of failure is improper positioning of the needle or catheter. Numerous illustrations of normal and abnormal angiograms are included. Typical case histories are presented. It is an essential part of the investigation of a space-occupying lesion in the kidney, of hydronephrosis, of congenital anomalies, and of any condition for which partial nephrectomy is contemplated. It is often desirable in suspected renal hypertension. The contraindications to its use are iodine sensitivity and uremia. Its scope will be increased by improvements in radiologic technics. It does not replace the standard well-tried urologic investigations, but is complementary to them.

MAXWELL

SURGERY AND CARDIOVASCULAR DISEASE

Bergy, G. G., and Bruce, R. A.: Discrepancies between Subjective and Objective Responses to Mitral Commissurotomy. New England J. Med. **253:** 887 (Nov. 24), 1955. Abstracted, Circulation **14:** 104 (July), 1956.

Cohen, M., Warden, H. E., and Lillehei, W.: A Technique for the Experimental Creation of Aorticopulmonary Fistula. J. Thoracic Surg. **30:** 66 (July), 1955.

The authors reported an experimental method for the production of a communication between the aorta and the pulmonary artery to simulate the rare condition of congenital aorticopulmonary fistula. The lesion was produced through a 2-stage procedure.

The first step consisted of placing a wafer of polyvinyl sponge, soaked in 4 per cent solution of diacetyl phosphate, between the root of the aorta and the pulmonary artery. This permitted the formation of a firm fibrous union between the origin of the 2 vessels.

In the second operation, a purse-string suture was placed in the anterior wall of the pulmonary artery, just above the pulmonary valve, and after this portion of the wall was excluded from the arterial lumen by a Satinsky clamp, it was incised. A cork-borer was introduced into the excluded segment, and the clamp was removed to allow it to enter the artery. Finally, the borer was moved in the direction of the aorta, to produce a defect between the 2 vessels at a point where they were firmly adherent.

ABRAMSON

Donovan, T. J., and Donovan, J. F.: Permanent Total By-pass of the Pulmonic Valve. J. Thoracic Surg. **30:** 1 (July), 1955.

The authors presented a follow-up study on dogs in which a permanent ligation of the main pulmonary artery had been produced and an extracardiac shunt had been substituted as a total by-pass of the pulmonic valve. The shunt consisted of plastic tube and venous homograft connecting the right ventricle to the main pulmonary artery, just distal to the occlusive ligature.

The animals were exercised on a treadmill, and it was noted that their exercise tolerance did not decrease over a 3-year period. This finding was interpreted as indicating that myocardial reserve had not been materially affected by the operation. It was concluded that despite the absence of a valve in the shunt, the method was well tolerated postoperatively both immediately and remotely. The possible application of this procedure to congenital cyanosis of cardiac origin was discussed.

ABRAMSON

Soutter, L., Scannell, J. G., and Myers, G. S.: Pneumonectomy and Pulmonary Valvulotomy in the Treatment of Active Tuberculosis and Pulmonary Stenosis. J. Thoracic Surg. **30:** 49 (July), 1955.

The authors presented the case of a male patient with advanced pulmonary tuberculosis and diabetes, who also had pulmonary stenosis and an interarterial septal defect. Despite the presence of the other disorders, surgical treatment of the congenital abnormalities was considered advisable.

Because of the fact that the tuberculous process was located in the left side of the chest, the heart was explored through this approach. The pulmonary stenosis was corrected with a Brock valvulotome followed by dilatation. At the same time a pleuropneumonectomy was performed.

After a stormy postoperative course, the patient recovered completely. The cyanosis and dyspnea were greatly improved.

ABRAMSON

Potts, W. J., Gibson, S., Berman, E., White, H., and Miller, R. A.: Surgical Correction of Tetralogy of Fallot. J A. M. A. **159:** 95 (Sept. 10), 1955.

The authors discuss 6-to-8-year postoperative results in the first 100 cases of aortic-pulmonary anastomosis for relief of cyanosis due to tetralogy of Fallot. This operation differs from one originally devised by Blalock and Taussig, in that blood is shunted into the pulmonary circulation directly from the aorta instead of by means of the subclavian artery. The authors have been able to follow every living patient in the first 100 consecutive patients operated on in Children's Memorial Hospital in Chicago. The results 6 to 8 years after operation were good in 68 per cent of the patients and fair in 16 per cent. One patient was classified as having poor results and 1 was unchanged. Fourteen patients have died; 5 of these improved after operation but died later. The hospital mortality was 9 per cent.

KITCHELL

Bahnson, H. T.: Excision of Aortic Aneurysms. J. Chron. Dis. **2:** 110 (July), 1955.

The treatment of aortic aneurysms by resection and reconstruction of aortic continuity is discussed.

Aortic aneurysms of all types are in most instances amenable to excision. Those due to syphilis, and the uncommon traumatic or mycotic aneurysms, are usually saccular with a relatively narrow mouth. Although they occur most commonly in the thoracic aorta where crossclamping of the aorta is possible for only a short period, the mouth of the aneurysm can usually be isolated, clamped, and the aneurysm excised. Arteriosclerotic aneurysms, although commonly fusiform in nature, fortunately arise almost invariably in the terminal portion of the abdominal aorta, where the parent vessel may be clamped above and below, the aneurysm excised, and a graft used to reconstruct the lumen.

Of the 2 general types of aneurysms, those due to syphilis are likely to be more dangerous to the patient because of interference with function of the thoracic organs in close proximity to the aorta. Prior to the use of modern drugs the interval from onset of symptoms to death was significantly less than 1 year in a majority of the patients. There is every reason to believe that with adequate antibiotic treatment following excision of the syphilitic aneurysm, the remaining aorta will function satisfactorily for many years. Less than 5 per cent of arteriosclerotic aneurysms extend to involve the region of the renal arteries or above. Since the aneurysms are limited to the terminal portions of the aorta, there is no reason to believe that swelling will recur when the aneurysm is replaced by a graft from an individual, in some instances 50 years younger than the recipient. Little or no danger is encountered by crossclamping the abdominal aorta distal to the renal arteries, provided one prevents dislodgment of clot from the aneurysm to the distal circulation or the occurrence of thrombosis in the stagnant iliac arteries during occlusion of these structures.

Operative mortality currently is approximately 25 per cent. This can be lowered by more judicious selection of patients. Arteriosclerotic aneurysms occur in older individuals in whom disease due to arteriosclerosis is a constant threat. Despite this threat, the risk of rupture of the arteriosclerotic aneurysm within 1 year is greater than the risk of operation. Among grafts used to reconstruct aortic continuity are homologous aortic grafts, either frozen or lyophilized, and synthetic fabrics.

MAXWELL

Gertner, S. B., Little, D. M., Jr., and Bonnycastle, D. D.: Urinary Excretion of Arfonad by Patients Undergoing "Controlled Hypotension" during Surgery. Anesthesiology **16:** 495 (July), 1955.

In 7 female patients undergoing "controlled hypotension" during surgery with intravenous Arfonad, the urinary excretion of the drug was measured colorimetrically by the method of Mitchell and Clark. No detectable amounts of drug were found in samples collected after the first 3 postoperative hours, and an average of 31 per cent of the total doses administered was recovered within this period, indicating that a considerable amount of the total dose of Arfonad given intravenously is excreted quite rapidly. Biologic assay of the urine showed that the drug was present in a biologically active form, retaining its potent and brief ganglionic activity. The fate of the remaining two thirds of the drug in human subjects is unknown. In several experiments in cats, the kidneys and liver do not appear to play any role in the destruction of Arfonad. Arfonad is probably destroyed rapidly after administration or at least is rapidly rendered inactive within the body by some as yet undetected mechanism.

SAGALL

Bruce, R. A., Merendino, K. A., Dunning, M. F., Scribner, B. H., Donohue, D., Carlsen, E. R., and Cummins, J.: Observations on Hyponatremia Following Mitral Valve Surgery. Surg., Gynec. & Obst. **100:** 293 (March), 1955.

Unexpected morbidity in some patients following mitral valve surgery stimulated the authors to investigate hyponatremia as a cause. They found hyponatremia of less than 127 mEq. per liter during the second to fourth postoperative days in 30 per cent of the patients. This occurred despite administration of saline and a positive sodium balance. Restricting fluid intake to less than a liter per day generally prevented the appearance of this state.

The authors concluded that the postoperative hyponatremia resulted from cardiac insufficiency and a positive water balance. The unrestricted administration of water during the early postoperative period was considered deleterious.

ABRAMSON

Haller, J. A., Jr., and Morrow, A. G.: Experimental Mitral Insufficiency: An Operative Method with Chronic Survival. Ann. Surg. **142:** 37 (July), 1955.

After studying several approaches, the authors consistently produced mitral insufficiency in dogs by severing chordae tendineae. This was accomplished by inserting a cutting hook through the left ventricular wall and engaging one or two of these structures.

Dogs with dyspnea only on exercise usually recovered from the operation, while those with dyspnea at rest died from pulmonary edema within three days.

ABRAMSON

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7–9170

AHA GRANTS MILLION DOLLARS FOR RESEARCH

Grants-in-aid support of more than $1,000,000 to aid 180 research projects in or related to the cardiovascular field have been announced by the American Heart Association. The awards, which total $1,042,817, cover the fiscal year beginning July 1, 1956 and continuing through June 30, 1957.

Fifty-one of the allocations are continuing grants while 129 are new awards. With the 130 previously announced fellowships and investigatorships, the grants bring the total number of American Heart Association research support awards made this year to 310; and the total amount of money awarded during the year now exceeds $1,870,000. This compares with 1955 allocations of $1,414,000 for 260 awards. In addition state and local Heart Association awards in 1955 added $2,382,781 to research money allocated from public contributions to the Heart Fund. State and local awards for 1956 will not be known until the end of the year.

A complete list of grants-in-aid follows at the end of this section.

SEPTEMBER 15 IS DEADLINE FOR AHA FELLOWSHIP APPLICATIONS

Applications for the Association's fellowship and investigatorship awards to be made in support of research to be conducted during the fiscal year, July 1, 1957 to June 30, 1958, must be submitted by September 15, 1956. Deadline for applying for grants-in-aid for the same period is November 1, 1956.

Following are descriptions of the types of awards involved:

Established Investigatorships: Awarded for periods of up to five years, subject to annual review, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. Initial stipend is $6,000 with an annual increment of $500.

Research Fellowships: To individuals with M.D. or Ph.D. degrees for periods of 1 to 2 years to enable recipients to obtain further research experience under supervision of senior investigators. Initial stipends range from $3,500 to $5,000 with exact amount determined largely by number of dependents. There is a modest increase after 1 year.

Grants-in-Aid: To experienced investigators to provide support for specific research projects. They are usually made for periods of 1 to 3 years.

Further information and application forms may be obtained from the Medical Director, American Heart Association, 44 East 23 Street, New York 10, N. Y.

AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS

Invitations to deliver the Lewis A. Conner and George E. Brown Memorial Lectures have been accepted by 2 distinguished leaders in the cardiovascular field. The lectures are traditional highlights of the Association's Scientific Sessions which this year are to be held in conjunction with the 32nd Annual Meeting in Cincinnati, October 26–November 2.

The Conner Lecture will be delivered by Jesse E. Edwards, M.D. of the Mayo Clinic. Dr. Edwards will discuss the physiopathologic characteristics of the pulmonary vessels in various congenital cardiac abnormalities. Hugh Montgomery, M.D., University of Pennsylvania, will deliver the Brown Lecture on oxygen tension of tissues in vivo. These lectures will be included in the Scientific Sessions programs on Saturday and Sunday mornings, October 27 and 28.

The Scientific Sessions programs, which ge

nderway on Friday evening, October 26 and continue through Monday, October 29, will also include presentations of original papers at both general morning sessions and simultaneous specialized afternoon sessions, 4 symposia or panel discussions, including 1 on *Cardiac Rehabilitation* to be conducted by the Association's Council on Community Service and Education, scientific and technical exhibits and medical films. Most of the scientific program will be presented at the Cincinnati Music Hall, while other portions will be conducted at the Netherland Plaza Hotel. The hotel will also house the Annual Meeting programs later in the week and serve as American Heart Association headquarters throughout the stay in Cincinnati.

Among the week's social events will be the Annual Dinner of the Association at the Netherland Plaza, Sunday evening, October 28. Registration forms for both Scientific Sessions and Annual Meeting are now available from the Association. These forms carry a list of available hotel accommodations and space to make necessary reservations. Address requests to the American Heart Association, 44 East 23 Street, New York 10, N. Y.

ECG TEST BOOK WELL RECEIVED

Initial professional response to the *Electrocardiographic Test Book* published by the Association and introduced at the 1956 Scientific Assembly of the American Medical Association has been unusually favorable.

The 2-volume *Electrocardiographic Test Book* includes 119 electrocardiograms, each of which is accompanied by specific questions, a series of 230 general questions on electrocardiography, and tables of normal values. The second volume contains answers to the questions and discussions of the tracings. Preparation of the work was undertaken by Travis Winsor, M.D., Los Angeles.

Copies of the *Electrocardiographic Test Book* may be obtained from the Medical Division, American Heart Association, 44 East 23 Street, New York 10, N. Y. Cost of the 2-volume set is $5.00.

COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH PROCEEDINGS

The *Proceedings* of the 1955 Annual Meeting of the Council for High Blood Pressure Research of the American Heart Association are now available. The 160-page volume is greatly expanded over the Council's meeting reports published in previous years. It includes all 8 papers presented at the meeting in Cleveland together with verbatim transcripts of ensuing discussions. Emphasis at the meeting was placed on the neurovascular aspects of hypertension.

The *Proceedings* may be obtained at a cost of $4.50 per copy. In addition, a special combined price of $7.50 has been set for those wishing to purchase a set containing the proceedings of the 1952, 1953, 1954 and 1955 meetings of the High Blood Pressure Research Council. Orders should be addressed to the Medical Director, American Heart Association, 44 East 23 Street, New York 10, N. Y.

LIFE INSURANCE FUND ANNOUNCES RESEARCH AWARD DEADLINES

Applications for research fellowships and grants-in-aid for the fiscal year beginning July 1, 1957, are now being accepted by the Life Insurance Medical Research Fund.

The postdoctoral fellowships carry a minimum stipend of $3,800 plus dependency and travel allowances. While applicants may be working in any of the medical sciences, preference will be given to those whose investigations deal with cardiovascular function or disease or related fundamental problems. Applications deadline is October 15, 1956.

Grants-in-aid will be made to institutions in support of cardiovascular and related research. Deadline for applying for these awards is November 1, 1956.

Further information and applications for all awards may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46 Street, New York 17, N. Y.

U.S.P.H.S. ANNOUNCES NEW GRANTS PROCEDURE

The United States Public Health Service has announced that applications for research grants

which do not exceed $2,000 plus indirect costs will henceforth be processed on a year-round basis, provided that the applicants do not seek support more than once a year. This will mean that applicants for this type of aid need not concern themselves with the usual applications deadlines. Action on applications can be expected within from 1 to 4 months of submission.

Additional information and applications may be obtained from the Division of Research Grants, National Institutes of Health, Bethesda 14, Md.

U.S. PHYSICIANS INVITED TO INTERNATIONAL CONGRESSES

Attendance of United States physicians will be welcomed at the Fifth Inter-American Congress of Cardiology in Havana, November 11–17. Registration forms for the Congress are now available from the Medical Director of the American Heart Association (44 East 23 Street, New York 10, N. Y.). An exhibit of the A.H.A. services to the medical profession will be on display at the Congress.

Medical scientists from this country have also been invited to 2 other international meetings of particular interest to those working in the cardiovascular field. These are the Latin American Congress of Angiology in Havana, November 8–10, and the Second European Congress of Cardiology in Stockholm, September 10–14. Additional information on this last meeting may be obtained from Dr. Karl Erik Grewin, Secretary General, Second European Congress of Cardiology, Södersjukhuset, Stockholm, Sweden.

MEETINGS CALENDAR

August 26–September 1: Congress of International Society of Hematology, Boston. Dr. W. C. Moloney, 39 Bay State Road, Boston, Mass.

August 29–September 2: Congress of the International Society for Blood Transfusion, Boston. Dr. J. Julliard, Secretary General of Society, 57 Boulévard L'Auteuil, Boulogne-sur-Seine, France.

September 6–8: American Association of Obstetricians and Gynecologists, Hot Springs, Va. F. R. Lock, Bowman Gray Medical School, Winston-Salem, N. C.

September 8–10: Symposium on Electrolytes and the Circulation. Sponsored by the Vermont Heart Association and the University of Vermont College of Medicine, Burlington, Vt. Dr. Eugene Lepeschkin, University of Vermont College of Medicine, Burlington, Vt.

September 9–13: Congress of the International College of Surgeons (including Annual Congress of the U. S. and Canadian Sections), Chicago. Karl Meyer, M.D., 1516 Lake Shore Dr., Chicago, Ill.

September 9–14: International Congress of Clinical Chemistry, New York. Dr. John G. Reinhold, 711 Maloney Bldg., University of Pennsylvania, Philadelphia 4, Pa.

September 10–14: American Congress of Physical Medicine and Rehabilitation, Atlantic City. Frances Baker, M.D., 1 Tilton Ave., San Mateo, Calif.

October 6–13: College of American Pathologists, Chicago. Arthur H. Dearing, 203 N. Wabash Ave., Chicago 1, Ill.

October 7–12: American Society of Clinical Pathologists, Chicago. C. G. Culbertson, 1040 W. Michigan St., Indianapolis 6, Ind.

October 8–12: American Society of Anesthesiologists, Kansas City, Mo. J. E. Remlinger, Jr., 188 W. Randolph St., Chicago 1, Ill.

October 8–12: American College of Surgeons, San Francisco. Michael L. Mason, 40 E. Erie St., Chicago 11, Ill.

ABROAD

September 10–14: Second European Congress of Cardiology, Stockholm. Professor K. E. Grewin, Södersjukhuset, Stockholm, Sweden.

September 19–23: International Congress of Internal Medicine, Madrid. Professor Dr. Carlos Jimenez Diaz, Facultad de Medicina, Madrid, Spain.

September 28–29: International Professional Union of Gynecologists and Obstetricians, Madrid, Spain. Dr. Jacques Courtois, St. Germain-en-Laye, Seine-et-Oise, France.

October 9–15: General Assembly of the World Medical Association, Havana. Dr. L. H. Bauer, 345 E. 46 St., New York, N. Y.

LIST OF GRANTS

Following is a complete list of recipients of 1956 grants-in-aid awarded by the American Heart Association, together with the institutions the scientists are working at and the subjects of their studies:

Continued Grants

Jerry K. Aikawa, University of Colorado School of Medicine, Denver. Immunophysiology.

Frederick W. Barnes, Jr., The Johns Hopkins Hospital, Baltimore. Regenerative cellular response to induced depletion of cellular proteins.

Gerhard A. Brecher, College of Medicine, Ohio State University, Columbus. Dynamic aspects of blood flow in physiological and pathological states.

F. Curtis Dohan, University of Pennsylvania, Philadelphia. Urinary excretion of specific α-ketolic steroids in "normal" individuals of various age groups.

Douglas R. Drury, Kerckhoff Laboratories, Los Angeles. Genetic and environmental factors in production of hypertension; cardiovascular responses and effects of lowering blood pressure in colony of spontaneously hypertensive rabbits.

Isidore S. Edelman, University of California, Metabolic-Isotopic Laboratory, San Francisco. Fluid and Electrolyte anatomy in patients with essential hypertension.

Allan V. N. Goodyer, Yale University School of Medicine, New Haven. Hemodynamic factors affecting metabolism and renal excretion of electrolytes; influence of electrolyte abnormalities on circulatory response to stress.

Arthur S. Guyton, University of Mississippi School of Medicine, Jackson. Development of methods for continuous recording of cardiac output.

John W. Hall, New York University College of Medicine, New York. Inflammatory response to autologous tissue.

John K. Hampton, Jr., Tulane University School of Medicine, New Orleans. Cardiovascular and metabolic adjustments of the rat concerned with development of resistance to physical trauma in Noble-Collip Drum.

K. Albert Harden, Howard University School of Medicine, Washington, D. C. Effect of chronic pulmonary disease and chest surgery upon pulmonary and cardiac function.

Mary Ellen Hartman, Temple University School of Medicine, Philadelphia. Quantitation of capillary responses in the mammalian glomerulus under normal and experimental conditions.

Edwin P. Hiatt, University of North Carolina School of Medicine, Chapel Hill. Effect of partial substitution of the nitrate ion for the chloride ion on circulation and electrolyte balance with special reference to hypertension and edema.

Theodore H. Ingalls, Harvard University School of Public Health, Boston. Laboratory and epidemiologic investigation of congenital heart disease.

Roger W. Jeanloz, Massachusetts General Hospital, Boston. Biological significance of the sulfate group in heparins.

Louis N. Katz, Medical Research Institute, Michael Reese Hospital, Chicago. Coronary circulation, cardiac energetics and myocardial metabolism.

Ancel Keys, University of Minnesota, Minneapolis. Relation between mode of life, particularly diet and physical activity, to the development of degenerative heart disease, as exemplified in different populations.

Walter M. Kirkendall, State University of Iowa College of Medicine, Iowa City. Effects of drug and surgical therapy on renal circulation and function in certain cardiovascular disorders.

Charles D. Kochakian, Oklahoma Medical Research Foundation, Oklahoma City. The role of steroid hormones in regulation of biochemistry of the heart.

Peter T. Kuo, University of Pennsylvania School of Medicine, Philadelphia. Vascular fluid dynamics, their influences upon intra-vascular distribution of plasmalipids and their relationship to problem of atherosclerosis.

Alfred Lazzarini, Jr., New York University, Post-Graduate Medical School, New York. Metabolic and immunological changes occurring in transplanted tissues.

Louis Leiter, Montefiore Hospital, New York. Use of a method of measuring lower extremity blood flow (muscle flow), to study peripheral circulation and to measure certain aspects of muscle metabolism in normal subjects and cardiac patients.

Eugene Lepeschkin, University of Vermont College of Medicine, Burlington. Differentiation between organic and functional systolic murmurs by means of esophageal calibrated phonocardiography, correlated with blood viscosity.

John P. Merrill, Peter Bent Brigham Hospital, Boston. The relation of renal failure to certain disorders of the cardiovascular system.

William F. Miller, University of Texas, Southwestern Medical School, Dallas. The development of an improved method of measuring arterial oxygen tension at all levels of oxygenation; and the role of oxygen in the treatment of acute pulmonary edema.

Wilfried F. H. M. Mommaerts, Western Reserve University, Cleveland. Chemical-physiological and biophysical studies related to the problem of contractility.

Robert E. Olson, University of Pittsburgh, Pittsburgh. Effect of congestive heart failure due to valvular disease upon myocardial metabolism in dogs.

Abraham G. Osler, Johns Hopkins University School of Hygiene and Public Health, Baltimore. Mechanism of hypersensitivity reactions.

David D. Rutstein, Harvard University Medical School, Boston. Effects of rheumatic fever serum and steroid compounds on human heart muscle in tissue culture.

David D. Rutstein, Cooperative Rheumatic Fever Study, American Heart Association, New York. Relative effectiveness of ACTH, cortisone and aspirin therapy of rheumatic fever in the prevention of rheumatic heart disease.

Carl F. Schmidt, University of Pennsylvania School of Medicine, Philadelphia. Physiology and pharmacology of coronary ciruclation, with special reference to influence of mechanical and nervous factors.

Bodil Schmidt-Nielsen, Duke University, Durham. Comparative studies on renal function in various animals with special emphasis on mechanism for

urea excretion as related to protein metabolism.

William B. Schwartz, New England Center Hospital, Boston. Acid-base regulation by the kidney and tissues.

B. H. Scribner, University of Washington School of Medicine, Seattle. Further studies on practical problems in the management of fluid electrolyte therapy.

Alvin P. Shapiro, Southwestern Medical School, University of Texas, Dallas. Controlled study in the rat of relationship between hypertensive vascular disease and experimental chronic pyelonephritis.

Thomas P. Singer, Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit. Succinic oxidase of the heart muscle; and mechanism of SO_2 fixation in animal tissues.

Jay A. Smith, Chicago Medical School, Chicago. Effect of various substances on the increase in metabolic rate due to ouabain as measured in cartesian diver.

Richard T. Smith, University of Minnesota, Minneapolis. Origin and significance of a heparin precipitable form of fibrinogen occurring in human rheumatic fever and other diseases, and experimentally in endotoxin treated rabbits.

Merrill P. Spencer, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C. Direct measurement of blood flow in humans.

Jeremiah Stamler, Michael Reese Hospital, Medical Research Institute, Chicago. Pathophysiological homeostasis of renal function and water-electrolyte metabolism in experimental congestive circulatory failure with edema.

Mario Stefanini, Saint Elizabeth Hospital, Brighton, Mass. Identification and purification of substances causing activation of fibrinolysin in man and their use in control and treatment of thromboembolic conditions.

Henry Swan, University of Colorado School of Medicine, Denver. Prevention and treatment of ventricular fibrillation during hypothermia.

Albert Szent-Gyorgyi, Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Mass. Chemical, macromolecular and histological structure of muscle and chemistry of contraction cycle; mechano-chemical coupling.

Lewis Thomas, New York University College of Medicine, New York. Mechanisms of tissue damage in bacterial infection and hypersensitivity.

William B. Wartman, Northwestern University Medical School, Chicago. Cytochemical changes that take place in the myocardium during injury, with special reference to ischemia and hypertrophy.

Levin Lyttleton Waters, Yale University School of Medicine, New Haven. Modification of the lesions of experimental atherosclerosis.

Stanford Wessler, Harvard Medical School at the Beth Israel Hospital, Boston. Intravascular coagulation induced by stasis and the clot acceleratin activity of serum (SPCA) under controlled condi tions; and analysis of the factors influencing thi mechanism.

Walter S. Wilde, University of Michigan School o Medicine, Ann Arbor. Effluographic determinatio of ion fluxes in heart muscle in relation to systol and the ECG.

Harrison Wood, Irvington House, Irvington-on Hudson, N. Y. Epidemiological studies of meth ods for prevention of rheumatic fever and rheu matic heart disease.

Irving S. Wright, New York Hospital, Cornel University Medical Center, New York. Electro static forces in blood coagulation and mode o action of ionic anticoagulants.

Marjorie B. Zucker, Sloan-Kettering Institute, New York. Mechanism of hemostasis, with particula reference to the effect of dextran and crystalline fibrinolysin.

New Approved Grants

Clarence M. Agress, University of California School of Medicine; Veterans Administration Center, Los Angeles. Use of proteolytic agents in acute myocardial infarction.

Ralph D. Alley, Albany Medical College, Albany, N. Y. Further evaluation of heterologous vascular shunts in aortic arch resection and long-term evaluation of aortic arch grafts.

Julian L. Ambrus, University of Buffalo School of of Medicine, Buffalo, Methods for quantitative evaluation of fibrinolysis in experimental coronary thrombosis produced with radioactive fibrin; and comparison of the effects of plasmin, heparin and dicumarol derivatives.

Edmund Bay, Tulane Medical School, New Orleans. Relationship between cardiac contractile force and ionic balance shifts.

David D. Becker, The New York Hospital-Cornell University Medical Center, New York. Physiologic effects of hypometabolism upon cardiovascular dynamics in patients with cardiac insufficiency.

Ellis S. Benson, University of Minnesota, University of Minnesota Hospitals, Minneapolis. Electron microscopic study of myocardium in heart failure.

Gerald S. Berenson, Louisiana State University School of Medicine, New Orleans. Effects of inflammatory reaction on biochemistry of connective tissue.

Maurice M. Best, Louisville General Hospital, Louisville. Serum lipid fractions in induced and spontaneous hypothyroidism and their modification b β-sitosterol.

Richard J. Bing, Washington University School o Medicine, St. Louis. Myocardial metabolism studies on contractile proteins of the failing hear

William S. Blakemore, Hospital of the University o

Pennsylvania, Philadelphia. Evaluation of freeze-dried homografts and synthetic cloth mesh materials used to replace human blood vessels.

Walter D. Block, University of Michigan, Ann Arbor. Fundamental investigation of the abnormal serum proteins of patients with primary systemic amyloidosis.

J. M. B. Bloodworth, Jr., Ohio State University, Columbus. Chemistry, histochemistry and renal histopathology of degenerative vascular disease associated with diabetes mellitus; a human and experimental study of the Kimmelsteil-Wilson Syndrome.

Lewis H. Bosher, Jr., Medical College of Virginia, Richmond. Bronchial artery circulation during various conditions of extracorporeal circulation.

Nancy M. Buckley, Albert Einstein College of Medicine, New York. Cardiodynamics and ventricular failure.

Henry M. Cavert, University of Minnesota Medical School, Minneapolis. Metabolism of cardiac tissue investigated with isotopic techniques; and intermediates of propionate, lactate, and pyruvate metabolism in cardiac tissue.

Fu-Chuan Chao, Stanford University, Stanford. Nucleoprotein in yeast, chick embryo and mammalian tissues.

Leon Churney, Louisiana State University School of Medicine, New Orleans. Electrical properties of normal and vagally inhibited auricular muscle.

Leland C. Clark, Jr., Fels Research Institute, Antioch College, Yellow Springs, O. Optimum conditions for maintaining brain oxygen supply during total by-pass of heart and lungs.

Hadley L. Conn, Jr., University of Pennsylvania Hospital and Medical School, Philadelphia. Utilization of radioisotope technic in study of cardiovascular pathological physiology.

Loyal Lee Conrad, University Hospital, Oklahoma City. Order of activation of the free wall of the right ventricle in experimental right-bundle-branch-block.

Jack W. Crowell, University Medical Center School of Medicine, Jackson, Mich. Effect of miliary embolism on circulatory dynamics.

R. Duncan Dallam, University of Louisville School of Medicine, Louisville. Certain biochemical responses of the various regions of the heart muscle to experimental hypo- and hyperthyroidism.

T. S. Danowski, University of Pittsburgh School of Medicine, Pittsburgh. Hemodialysis in chronic but-advanced but not terminal renal failure.

Clarence Dennis, State University of New York Medical College at New York City, Brooklyn. Use of the artificial heart-lung apparatus to support the failing circulation.

Ralph A. Deterling, Jr., Columbia University College of Physicians and Surgeons, New York. Long-term study of synthetic replacement of blood vessels; and prosthetic correction of aortic insufficiency.

Richard A. DeWall, University of Minnesota Medical School, Minneapolis. Development of a simple disposable oxygenator for use in intracardiac surgery.

Frank Dituri, Hospital of the University of Pennsylvania, Philadelphia. Antimetabolites to the biosynthesis of cholesterol.

Carl Djerassi, Wayne University, Detroit. Chemical studies on hypotensive alkaloids.

William Drell, University of California Medical Center and Veterans Administration Center, Los Angeles. Nature of the immediate precursors of sympathin.

Robert L. Driver, University of Vermont College of Medicine, Burlington. Influence of ions and temperature on intracellular distribution of drugs.

J. Russell Elkinton, Hospital of the University of Pennsylvania, Philadelphia. For studies on the supra-optico-hypophyseal system in the normal dog, cat, and rat pertaining to volume and concentration regulation; an effort to provide at least a partial explanation of certain phenomena observed in markedly edematous patients with heart disease; and a second grant for the study of body composition and extracorporeal dialysis in edematous patients with cardiovascular-renal disease.

Robert S. Ely, University of Utah College of Medicine, Salt Lake City. Evaluation of corticosterone metabolism in patients with rheumatic fever.

Franklin H. Epstein, Yale School of Medicine, New Haven. Factors influencing renal concentrating ability.

Alfred Farah, State University of New York, Upstate Medical Center, Syracuse. Factors influencing the treppe and after-stimulation contraction in cardiac muscle.

George Fawaz, American University of Beirut, School of Medicine, Beirut, Lebanon. Effect of Krebs cycle inhibitors and metabolites on the performance and metabolism of the isolated mammalian heart (Heart-lung preparation).

George A. Feigen, University of Oxford, Radcliffe Infirmary, Oxford, England. (1) Kinetic analysis of ventricular response to ATP, cardiac glycosides and other agents in presence of abnormal anions; (2) mechanism of anaphylactic contraction of intestinal muscle; (3) kinetics of immune hemolysis and sedimentation in enzyme-treated erythrocytes.

Frank A. Finnerty, Jr., Georgetown University School of Medicine, Washington, D. C. Cardiovascular evaluation of delirium tremens.

Alfred P. Fishman, Columbia University College of Physicians and Surgeons, New York. Relationships between ventilation and pulmonary blood flow in normal man and in patients with chronic cardio-pulmonary disease.

Noble O. Fowler, Emory University School of Medicine, Atlanta. To study the hemodynamic effects of plasma volume expansion.

Meyer Friedman, Harold Brunn Institute, Mount

Zion Hospital, San Francisco. Further studies concerning the metabolism of cholesterol.

Mario Gaudino, New York University College of Medicine, New York. Water and electrolyte exchanges in tissues.

William W. L. Glenn, Yale University School of Medicine, New Haven. Enzymatic dissolution of intravascular clots in the dog, including pulmonary and arterial embolus and thrombosis, both acute and chronic.

Robert A. Good, University of Minnesota, Minneapolis. To study the basic mechanisms involved in etiology and pathogenesis of rheumatic fever and related diseases.

Carl W. Gottschalk, University of North Carolina, Chapel Hill. Mammalian micropuncture study of some physical factors in kidney function.

Jacob Grossman and *Raymond E. Weston*, Montefiore Hospital, New York. Response of cardiac patients to mercurial diuretics with particular reference to tubular adaptations to reduced filtration rate in congestive heart failure; and cardiovascular-renal mechanisms regulating body fluid volume in man.

Robert E. Gross, The Children's Hospital, Boston. Studies relevant to surgical treatment of congenital heart disease.

Thomas R. Hamilton, University of Kansas School of Medicine, Kansas City. Community-type study of children in rheumatic and nonrheumatic families.

Calvin Hanna, University of Vermont Medical School, Burlington. Tachyphylaxis.

Walter Heymann, University Hospitals, Babies and Children's Division, Cleveland. Regulation of blood lipid concentration with special reference to pathogenesis of nephrotic hyperlipemia.

William C. Holland, Vanderbilt University School of Medicine, Nashville. For study of the mechanish of action of antifibrillatory drugs.

Joseph Paynter Holt, University of Louisville, Institute for Medical Research, Louisville. Venous system in dogs and man with special reference to "collapsibility" of veins, and how this effects pressure and flow through the venous system; and residual volume of the dog's ventricle.

Tom Hoshiko, University of Copenhagen, Copenhagen, Denmark. To study the chloride excretion by the renal tubules.

Richard J. Jones, University of Chicago School of Medicine, Chicago. For studies on the mode of action of hypocholesteremic agents.

Howard A. Joos, Childrens Hospital Society of Los Angeles, Los Angeles. Factors regulating blood pressure in infancy and childhood.

Alex Kaplan, Medical Research Institute, Michael Reese Hospital, Chicago. Role of adrenal medullary and cortical hormones in regulation of lipid metabolism.

Nathan O. Kaplan, McCollum-Pratt Institute, The Johns Hopkins University, Baltimore. Metabolic significance of nucleotides in cardiovascular tissues.

F. E. Kelsey, University of South Dakota Medical School, Vermillion. Mechanism of action of digitoxin and related substances.

Grace P. Kerby, Duke University School of Medicine, Durham, N. C. To study the metabolism of acid mucopolysaccharides of ground substance.

Paul Kezdi, Northwestern University Medical School, Chicago. To study the baroreceptor and sympathetic activity in renal hypertension in the dog.

Peter K. Knoefel, University of Louisville School of Medicine, Louisville. Extent and nature of the involvement of the kidney in certain changes in the dog's circulation.

Harvey C. Knowles, Jr., University of Cincinnati College of Medicine, Cincinnati General Hospital, Cincinnati. Occurrence and distribution of carotenoid pigments in atherosclerosis in humans.

Charles E. Kossman, New York University College of Medicine, New York. Correlation of intracellular potential variations of the single ventricular fiber with mechanical function of the ventricles.

William J. Kuhns, University of Pittsburgh Medical Center, Pittsburgh. Immunochemical studies of human diphtheria antitoxins—investigation of toxin-antitoxin complexes.

Willoughby Lathem, University of Pittsburgh School of Medicine, Pittsburgh. Glomerular permeability to hemoglobin.

Alexander Leaf, Harvard Medical School, Massachusetts General Hospital, Boston. The state of body water.

Maurice Lev, Mount Sinai Hospital of Greater Miami, Miami Beach. Histopathology of the conduction system in congenital heart disease.

David H. Lewis, Philadelphia General Hospital, Philadelphia. Transmission of sound and ultrasound in heart; use in measurement of chamber size, detection of congenital defects, and characterization of murmurs.

Averill A. Liebow, Yale University School of Medicine, New Haven. Quantitative comparative studies of experimentally induced collateral circulation to the heart.

Robert F. Loeb, Columbia University College of Physicians and Surgeons, New York. Relationships between ventilation and pulmonary blood flow in normal man and in patients with chronic cardiopulmonary disease.

William D. Lotspeich, University of Cincinnati College of Medicine, Cincinnati. Relation between intermediary metabolism in the kidney and several of its excretory functions.

Robert H. Maybury, University of Redlands, Redlands, Calif. Physical chemistry of proteins dissolved in nonaqueous solvents, including anhydrous hydrogen fluoride.

James W. McCubbin, Cleveland Clinic Foundation, Cleveland. Neural mechanisms in experimental renal hypertension.

Henry D. McIntosh, Duke University School of Medicine, Durham, N. C. Responses of pulmonary and systemic circulation to changes of intrathoracic pressure.

Henry C. McGill, Jr., Louisiana State University School of Medicine, New Orleans. Electron microscopy of vascular lesions.

Edward Meilman, Long Island Jewish Hospital, New Hyde Park, N. Y. Contractile apparatus in smooth muscle.

Milton Mendlowitz, The Mount Sinai Hospital, New York. Digital circulation in hypertension.

H. C. Meng, Vanderbilt University School of Medicine, Nashville. Production of lipemia clearing factor(s) and its role in lipid metabolism and atherogenesis.

William R. Milnor, Johns Hopkins University and Hospital, Baltimore. Regional blood volume in congenital and acquired heart disease.

Frederick C. Moll, University of Washington School of Medicine, Seattle. Isolation and description of the serum proteolytic enzyme inhibitor.

Ian W. Monie, University of California, Berkeley. Pathogenesis of cardiovascular anomalies in rat embryos from mothers deprived of pterolylglutamic acid (PGA) during part of pregnancy.

Merwin Moskowitz, Purdue University, Lafayette, Ind. Studies on an antigen of streptococci that binds on to tissues.

Jan Nyboer, Harper Hospital, Detroit. Adaptation of thermal devices to measurement of blood flow.

J. Lowell Orbison, University of Rochester, School of Medicine and Dentistry, Rochester, N. Y. Relationship of the kidney to membrane permeability and fluid and electrolyte distribution in experimental hypertensive cardiovascular disease.

John J. Osborn, Stanford University School of Medicine, San Francisco. Diagnosis and surgical treatment of congenital and acquired heart disease; extracorporeal circulation, gasometric analyses of flow and shunts; Cardiorespiratory physiology in open-chest surgery.

Jacques Padawer, Albert Einstein College of Medicine, Yeshiva University, New York. Physiology of mast cell and its relation to cardiovascular disease.

Robert G. Page, University of Chicago School of Medicine, Chicago. Studies of the electrolyte balance of the heart in the intact dog: (1) Effect of adrenal cortical substances; (2) mechanism of the therapeutic effect of potassium on digitalis induced arrhythmias.

Ely Perlman, Mount Sinai Hospital, New York. Role of tobacco allergy in the etiology of cardiovascular diseases.

Leslie H. Peterson, University of Pennsylvania School of Medicine, Philadelphia. Review of the status of theoretical fluid mechanics as it applies to hemodynamics and related computing; and foreign visits associated with the 20th International Physiological Congress.

Reno R. Porter, Medical College of Virginia, Richmond. Circulatory dynamic effects of digitalis in normal and hypervolemic dogs.

Jack A. Pritchard, University of Texas, Southwestern Medical School, Dallas. Acquired defects in the hemostatic system.

Francisco L. Raffucci, University of Puerto Rico School of Medicine, San Juan. Approach to the aortic valve and production of intracardiac shunt.

Simon Rodbard, University of Buffalo-Chronic Disease Research Institute, Buffalo. Dietary patterns in development and regression of experimental arteriosclerosis.

Ray H. Rosenman, Mount Zion Hospital, San Francisco. Mechanism of hypercholesteremia and hyperlipemia in experimental nephrosis in rats.

Abraham M. Rudolph, The Children's Medical Center, Boston. Pulmonary hypertension in congenital heart disease.

Robert F. Rushmer, University of Washington School of Medicine, Seattle. Factors influencing diastolic filling and systolic emptying of the ventricular chambers.

D. Rao Sanadi, University of California, Berkeley. Mechanism of α-ketoglutarate oxidation and coupled phosphorylation.

Allen M. Scher, University of Washington School of Medicine, Seattle. Body surface potentials produced by an intracardiac dipole.

Arthur J. Seaman, University of Oregon Medical School, Portland. Controlled long-term study of continuous anticoagulant therapy in coronary artery disease.

Arthur Selzer, Stanford University School of Medicine, San Francisco. Experimental production of cardiogenic shock; and hemodynamic effects of 1-norepinephrine with special reference to cardiogenic shock.

Alan C. Siegel, Northwestern University, Children's Memorial Hospital, Chicago. Incidence, diagnosis, treatment and nonsuppurative complications of group A streptococcal infections in a general pediatric population, with particular reference to the attack rate and prevention of rheumatic fever.

Herbert O. Sieker, Duke University School of Medicine, Durham, N. C. Study of pressure in venous and pulmonary circulation using a miniature manometer catheter.

Daniel H. Simmons, Veterans Administration Center, West Los Angeles. Role of the bronchomotor tone in etiology of cor pulmonale.

Marvin D. Siperstein, University of Texas, Southwestern Medical School, Dallas. For the studies on factors influencing the destruction of cholesterol.

Paul W. Smith, University of Oklahoma School of

Medicine, Oklahoma City. Protection of the heart from fibrillation at subnormal body temperatures.

Harry Sobel, University of Southern California and the Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles. For an investigation of cellular proteins of heart muscle.

Sheldon C. Sommers, Massachusetts Memorial Hospitals, Boston. Histochemistry and ultraviolet microscopy of kidney, adrenal and vascular tissues from persons with essential hypertension.

Paul Starr, University of Southern California, Los Angeles. Effect of thyroid hormone on cardiovascular system: triiodothyronine.

Chandler A. Stetson, Jr., New York University College of Medicine, New York. In vitro studies on delayed or bacterial hypersensitivity.

Borys Surawicz, Mary Fletcher Hospital and Bishop De Goesbriand Hospital, Burlington, Vermont. Negative after-potential of the mammalian heart.

Adolph Surtshin, Washington University School of Medicine, St. Louis. Protective effect of protein depletion on mercury poisoning and on action of mercurial diuretics.

Roy C. Swan, Cornell University Medical College, New York. Measurement of extracellular fluid volume.

Leon Swell, Veterans Administration Hospital, Martinsburg, W. Va. Mechanism of cholesterol absorption and its regulation in the blood.

Helen B. Taussig, Cardiac Clinic, Harriet Lane Home, Johns Hopkins Hospital, Baltimore. Etiology of congenital malformations of heart and great vessels.

C. Bruce Taylor, Presbyterian Hospital, Chicago. Atherosclerosis and lipid metabolism in the rhesus monkey and comparative studies in man.

Henry L. Taylor, Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis. Physical activity and degenerative heart disease, particularly the use of railroad retirement board records to study death rates from degenerative heart disease among active and sedentary railroad employees.

Louis Tobian, University of Minnesota School of Medicine, Minneapolis. Physiology of the renal antihypertensive mechanism in man and experimental animals.

John C. Vanatta, University of Texas, Southwestern Medical School, Dallas. Further investigation of 2 intracellular sodium compartments which have been demonstrated in studying muscle biopsies after radioactive sodium, and radioactive sulfate injections.

Kurt N. von Kaulla, University of Colorado School of Medicine, Denver. Fibrinolytic enzymes.

Richard W. Von Korff, University of Minnesota Medical School, Minneapolis. Intermediary metabolism of cardiac muscle.

George E. Wakerlin, University of Illinois College of Medicine, Chicago. Pathogenesis and treatment of experimental hypertension produced by constriction of carotid sinus area.

Homer R. Warner, University of Utah, Salt Lake City. Physiology of the mammalian heart during complete by-pass.

John M. Weller, University of Michigan Medical School, Ann Arbor. Abnormalities of electrolyte metabolism and acid-base balance in hypertension.

William J. Whelan, University of California Medical Center, Los Angeles. Cardiac efficiency.

Charles M. Wilhelmj, Creighton University School of Medicine, Omaha. Diet, emotional tension and the autonomic nervous system as etiologic factors in hypertension.

Robert A. Woodbury, University of Tennessee Medical Units, Memphis. Drug action on cardiac muscle with special attention to mechanism of action; sympathomimetic amines and serotonin will be studied, using the papillary muscle technique.

Felix Wroblewski, Sloan-Kettering Institute for Cancer Research, New York. Serum enzymes in relation to experimental and clinical heart disease.

Paul N. Yu, University of Rochester School of Medicine, Rochester, N. Y. Pharmacodynamics of the pulmonary vascular resistance in man.

Benjamin W. Zweifach, New York University-Bellevue Medical Center, New York. Delineation of physical and chemical factors affecting blood flow and trans-capillary exchange.

CONTRIBUTORS TO THIS ISSUE

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